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Medical, Surgical, and Gynecologic Complications of Pregnancy

Sheldon H. Cherry, M.D., Guest Editor

Commemorating the 25th anniversary of *Rovinsky & Guttmacher,* classic Mount Sinai Medical Center textbook, and the publication of the 3rd edition, edited by Sheldon H. Cherry, M.D., Richard L. Berkowitz, M.D., and Nathan G. Kase, M.D.

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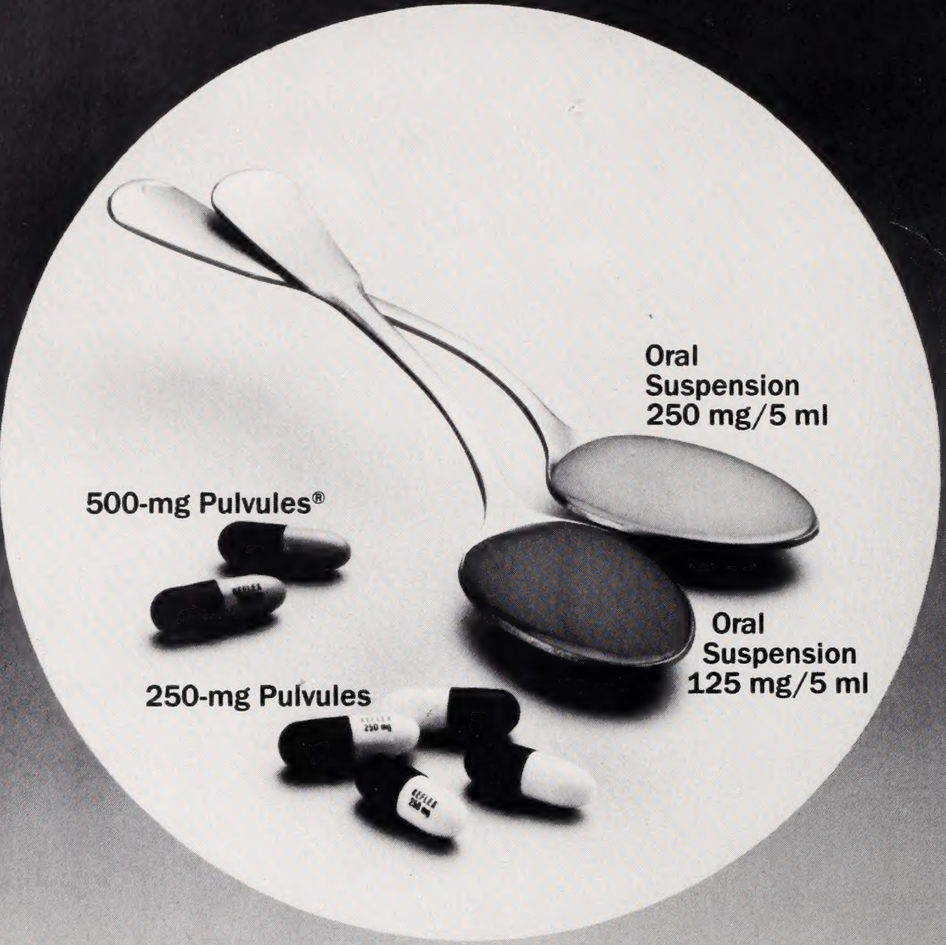
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CONTENTS

MEDICAL, SURGICAL, AND GYNECOLOGIC COMPLICATIONS OF PREGNANCY

Introduction *Sheldon H. Cherry, M.D.* 1

Joseph J. Rovinsky, M.D. 2

Foreword to Third Edition *Saul B. Gusberg, M.D., D.Sc., FACS, FACOG, FRCOG* 3

Immunology of Pregnancy *Bernard R. Adelsberg, M.D.* 5

Endocrinology of Pregnancy *Nathan G. Kase, M.D., and J. Victor Reyniak, M.D.* 11

Clinical Aspects of Gestational Trophoblastic Diseases *Carolyn D. Runowicz, M.D.* 35

Hypertension in Pregnancy *Frank A. Chervenak, M.D., and Richard L. Berkowitz, M.D.* 46

Thyroid Disease in Pregnancy and the Postpartum Period *Terry F. Davies, M.D., and Rhoda Cobin, M.D.* 59

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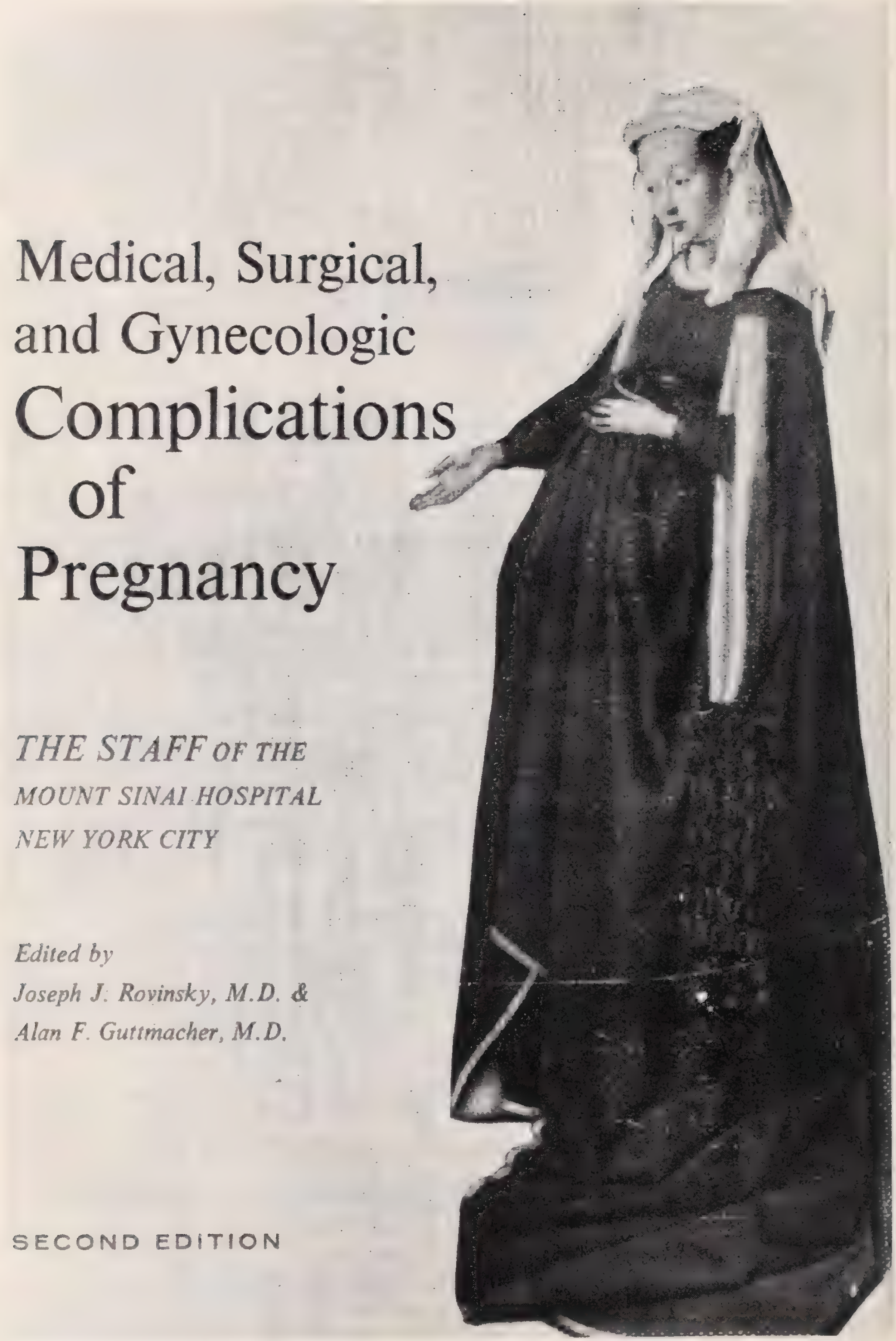

Medical, Surgical,
and Gynecologic
Complications
of
Pregnancy

THE STAFF OF THE
MOUNT SINAI HOSPITAL
NEW YORK CITY

Edited by
Joseph J. Rovinsky, M.D. &
Alan F. Guttmacher, M.D.

SECOND EDITION

The cover of the second edition. Reprinted with permission from *Rovinsky and Guttmacher's Medical, Surgical, and Gynecologic Complications of Pregnancy*, 2nd ed., copyright 1965, Baltimore; Williams & Wilkins.

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Medical, Surgical, and Gynecologic Complications of Pregnancy

Introduction

> The interplay between obstetrics and the other fields of medicine is more extensive and intimate than in any other specialty. This stems from the fact that pregnancy represents a unique condition in the health cycle, unique in the first place because pregnancy creates a profound, temporary alteration of physiology which may rapidly deteriorate into a state of pathology; unique in the second place because pregnancy represents a physiologic state which by the will of man can be prevented or, once begun, acutely terminated. In the third place, it is the only chapter of medicine in which the interests of two patients are so inextricably intertwined, interests occasionally antagonistic.
>
> —*Rovinsky & Guttmacher, 1960*

This issue of *The Mount Sinai Journal of Medicine* commemorates the publication of the third edition of *Rovinsky and Guttmacher's Medical, Surgical, and Gynecologic Complications of Pregnancy*. This is the twenty-fifth anniversary of the publication of the first edition, a landmark text in the obstetrical literature, significant in that it recognized and organized the multidisciplinary approach to the management of complicated pregnancies.

Dr. Guttmacher, as chief of the Department of Obstetrics and Gynecology of The Mount Sinai Hospital, was a leader in providing subspecialty consultation for pregnant women through specialty clinics such as cardiac, chest, hematology and psychiatry. The first edition was the result of this expertise. Its immediate success attested to its valuable and unique contribution. All of the contributors were Mount Sinai Hospital staff, demonstrating the institution's depth of clinical expertise during the era before the medical school. In 1965 Dr. Rovinsky, currently chief of Obstetrics and Gynecology at Long Island Jewish Hospital, took over the editorship for the updated 2nd edition.

The first edition, by realizing the objective outlined in its preface, presaged the development of the obstetrical subspecialty of perinatology. In the 25 years since that edition, major changes have occurred in our specialty. During those 25 years, maternal mortality has decreased 4 to 5 times and perinatal mortality has decreased 2 to 3 times.

Perinatology probably started with the work of Dr. William Lily, a brilliant New Zealand obstetrician. He developed the first accurate method for diagnosing a fetal condition in utero, namely amniotic fluid bilirubin studies in Rh disease of pregnancy. He then went on to develop the first method for treating a fetus in utero, intrauterine fetal transfusion.

Since then, advances in ultrasonography, genetics, fetal endocrinology and metabolism, fetal monitoring, fetoscopy and fetal therapy have increased our ability to diagnose and treat the "other patient" or "second patient," the fetus.

The three editions of *Medical, Surgical, and Gynecologic Complications of Pregnancy* have paralleled the regimes of three distinguished chiefs of Obstetrics: Alan Guttmacher, Saul Gusberg, and Nathan Kase. Dr. Guttmacher built Mount Sinai's obstetrics service into one of the finest clinical services in the city. Dr. Gusberg started the Medical School department and encouraged the growth and development of the full-time academic service. Dr. Kase has initiated and enhanced strong academic subspecialty departments such as perinatology and reproductive endocrinology.

This new, third edition sustains the tradition that each contributor is a member of the Medical Center staff, reflecting sentiment as well as the growth and development of The Mount Sinai Medical Center. A few representative chapters have been selected for this issue of the *Journal*. These chapters discuss some of the newer areas covered in the comprehensive 61 chapters by 101 contributors.

This editor wishes to thank Doctors Berkowitz and Kase, his co-editors, for their help and guidance, as well as all the other contributors to this Mount Sinai textbook.

SHELDON H. CHERRY, M.D.
Associate Clinical Professor
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The publication after a hiatus of twenty years of a third edition of *Medical, Surgical, and Gynecologic Complications of Pregnancy* as a creation of the staff of The Mount Sinai Medical Center is an exciting testament to the continuing and eclectic clinical excellence of the medical faculty and staff of the institution and to the foresight and acumen of the text progenitor, Dr. Alan F. Guttmacher (1898–1974).

Alan Guttmacher joined the staff of The Mount Sinai Hospital in 1952, after a distinguished twenty-five year career in obstetrics and gynecology in Baltimore, Maryland, where he was associate professor of obstetrics and gynecology at the Johns Hopkins School of Medicine. In New York, Alan became the first director of a combined Department of Obstetrics and Gynecology at The Mount Sinai Hospital, and clinical professor of obstetrics and gynecology at the College of Physicians and Surgeons of Columbia University. He introduced to The Mount Sinai Hospital, and perhaps to the country, the first obstetric service whose interest in and emphasis on maternal and fetal medicine was a unique and extremely farsighted contribution to the development of the specialty. It was exciting to participate with him in the creation of this innovative structure, to watch his stimulation of the interest of specialists in other fields of medicine in the problems posed and encountered by the parturient, and to see how the fine clinical and scientific talents of an entire institution when focused on areas previously ignored resulted not only in a marked improvement in the care of the pregnant woman but in the production of the first edition of a comprehensive text on the subject of maternal and fetal medicine. Pioneering work on intrapartum fetal monitoring, habitual abortion, and fetal distress was reported in this first edition, which also carried the first description in the medical literature of a syndrome now known under the term "intrapartum uterine growth retardation." It was Alan's dream that each child born not only be wanted and loved by its parents but be entitled to enter this world in optimal physical and mental state. The value of the work of the staff of The Mount Sinai Hospital was recognized by the wide acceptance of the first edition of this text (1960), by the appearance of a second edition in short order (1965), and by the translation and dissemination of the text of the second edition in Spanish and Portuguese editions.

There is little question that Alan Guttmacher's concept of a holistic approach to the pregnant patient was the seed which germinated to develop a quarter of a century later into the modern subspecialty of maternal fetal medicine. The institution itself is to be congratulated for permitting these concepts to flourish, and for the maintenance by the entire medical staff of a preeminent position in all fields, but most especially in reproductive medicine.

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Foreword to Third Edition

SAUL B. GUSBERG, M.D., D.SC., FACS, FACOG, FRCOG

In the past 20 years, two forces have been at work in changing the face of obstetrics: The naturalization of pregnancy and childbirth as a normal physiologic event has emerged as an important concept in young women of reproductive age, at the same time that a widening spectrum of scientific and technologic advance has conferred a deeper understanding of the endocrine, metabolic, and psychologic events of pregnancy and the aberration of these events in disease. Some imagine the humanistic and scientific spheres to be antipathetic. In fact, obstetricians have been sensitive to both forces, and modern obstetrical practice is a reflection of the fusion of these concerns that offer safety to mother and child and security to their family. Indeed, one might call this practice anthropology at the family level.

While reproductive medicine has become more scientific, it has also embraced the insights of medicine and surgery together with those of other clinical and basic disciplines. But these aspects of medicine have also been sharpened by the advance of biomedical research, and subspecialists in these areas have become increasingly expert in utilizing new concepts and new technology in their own refined focus. Thus, a spirit of competition and cooperation has arisen in the constant effort to offer mother and child the greatest expertise available.

As the captain of this medical team, the obstetrician must master some of these data that constitute the high risk obstetric constellation, while distilling and understanding the other concepts of diagnostic and therapeutic support that can be offered by special consultants. Thus, the seasoned clinicians and educators who have edited and authored this textbook have assembled the current information concerning medical and surgical disorders that can afflict pregnant women, so that the obstetric specialist can have available in one volume the expertise afforded by these authorities.

The art of medicine requires that we understand and support our patients' psycho-emotional needs, while the science of medicine demands that we be current in the many advances that enable us to offer those whose care is entrusted to us the best that modern medicine has to offer. This textbook will be a valuable asset for every physician who is engaged in the care of pregnancy and childbirth.

The author is Distinguished Service Professor and Chairman of Obstetrics and Gynecology Emeritus, The Mount Sinai Medical Center, New York.

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Medical, Surgical, and Gynecologic Complications of Pregnancy

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Immunology of Pregnancy

Bernard R. Adelsberg, M.D.

The maintenance of a normal human pregnancy requires the maternal immune system to perform a delicate balancing act. On the one hand, maternal recognition of fetal (paternal) antigens seems to be a prerequisite for carrying a placenta to term. On the other hand, a misdirected or too rigorous immune response may prevent conception and/or implantation or may cause serious intrauterine damage to the developing fetus. Nonspecific systemic immunosuppression of the mother would also be unlikely since it would be of little survival value to the species to have its reproductive females at greater risk particularly while carrying the next generation. Thus, it appears that the maternal immune system must be finely tuned to allow for a successful pregnancy.

The development of techniques to measure immune functions and capabilities has led to an explosion of information about the immunology of pregnancy. A 1979 review (21) cites more than 800 references reporting experiments on and observations of human and animal pregnancy. Research has continued, of course, and many other reports have appeared since then. This chapter will concentrate on maternal responses to pregnancy and will deal solely with information regarding human immune reactivity during pregnancy.

Reactions of the human immune system are often considered to be either cellular (lymphocyte mediated) or humoral (antibody mediated). There are multiple other facets to normal immune function including macrophage and polymorphonuclear leukocyte capabilities, reactivity of the clotting system and platelet function, complement system activation and a whole list of prostaglandin-mediated reactions. The explanation of how these interrelated mechanisms are altered to allow for pregnancy to be preserved is, as yet, incomplete but there does exist a body of experimental knowledge dealing with some of these areas.

The cellular or lymphocyte-mediated arm of the immune system has come under intense scrutiny. We now recognize two major classes of lymphocytes: T cells and B cells. B cells are lymphocytes that eventually go on to become plasma cells and whose primary function appears to be the manufacture of antibodies. T cells can be subdivided into groups with entirely different functions. There are T-helper cells that augment antibody production and cell-mediated immune reactions such as the generation of lymphokines. There are T-suppressor cells that inhibit these reactions. There are T cells that are cytotoxic to other cells either naturally, as the "natural killer" cells, or after antibody has bound to the cell as the cells responsible for antibody-dependent cell-mediated cytotoxicity. As well as having different functions, these cells express on their surfaces unique antigenic determinants that allow for their detection and separation. We can recognize these different cell types by a variety of in vitro and in vivo tests. B and T cell numbers can be measured in the circulation by removing heparinized plasma from the patient and separating the lymphocytes by gradient centrifugation on Ficoll-Hypaque. They are then incubated with fluorescein-labeled monoclonal antibodies known to recognize cell surface determinants specific for B cells, T cells, macrophages, etc. The fluorescence-positive cells are then counted using an indirect fluorescence microscope. The function of B cells can be quantitated in vitro by their proliferative response to pokeweed mitogen. In fact, the entire humoral limb of the immune system may be tested in vivo by immunization. A vigorous antibody response to vaccination with tetanus, ty-

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From the Division of Clinical Immunology, Department of Medicine, The Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029. Address reprint requests to the author there.

phoid or pneumococcal antigens implies that the entire humoral response from macrophage to plasma cell is intact. Likewise, functional tests for cell-mediated immunity can be tested in vivo and in vitro. Laboratory tests for T cell activity include proliferative responses to mitogens (phytohemagglutinin [PHA] and concanavalin A [Con A]), and antigens (*Candida,* purified protein derivative [PPD], streptokinase-streptodornase [SKSD], etc.), as well as tests for the production of lymphokines (migration inhibition factor, lymphocyte inhibition factor, interferon, etc.). There are also separate tests for "natural killer" cell activity and antibody-dependent, cell-mediated cytotoxicity. In vivo tests include measurement of skin reactivity to recall antigens such as *Candida,* SKSD, PPD, and mumps, and sensitization of the patient to a new antigen, dinitrochlorobenzene (DNCB). Thus, in our consideration of the immunology of pregnancy, we may find that our inability to be definitive about the immune system itself indicated by the plethora of tests complicates our understanding of how it functions in pregnancy.

Humoral Immunity

The first topic to be discussed is the effect of pregnancy on the humoral immune system. The plasma levels of IgG, IgM, and IgA throughout pregnancy have been found to be normal (22), although there is another report indicating that IgG levels decrease in the third trimester possibly due to placental transfer (27). Pregnant women have been immunized with typhoid vaccine (2) and tetanus vaccine (23, 28) with good responses noted. Antibody levels to streptococcal and staphylococcal antigens have also been determined during pregnancy and show no alteration in response when compared to nonpregnant controls (53). The Committee on Infectious Diseases of the American Academy of Pediatrics has, in fact, published recommendations for immunization during pregnancy and suggests that it is safe and effective. Relatively high doses of vaccine are used, however—from 6 to 10 times the standard dose. These higher doses appear to be necessary to protect, i.e. immunize, the child, but are not necessary to induce immunization in the mother (48).

Responses to endogenous as well as exogenous antigens are a frequent occurrence in normal pregnancies. Red cells may leak from the fetal circulation into the maternal circulation and stimulate the production of anti-Rh antibodies (41) or anti-A or anti-B antibodies under the appropriate circumstances. IgG antibodies against platelets may be responsible for neonatal thrombocytopenia if the appropriate circumstances for sensitization occur.

Fetal lymphocytes are also an excellent source of antigenic determinants to which the maternal immune system may respond. Anti HLA-A, B and C antibodies may be detected in the serum of as many as 30% of women undergoing their first pregnancy (14). Antibodies with activities against HLA-D antigens have also been discovered in pregnant women (54). These antibodies are important both to map B cell polymorphism and to study the mixed lymphocyte response (MLR) since HLA-D antigens are believed to be involved in recognizing "foreign" cells and initiating the MLR. These maternal antibodies seem to be able to inhibit this reaction. Their specificity and importance for a normal pregnancy will be discussed later. Antibodies directed against non-HLA determinants on lymphocytes, lymphoblastoid cells and other transformed cells, have also been described (17, 49).

Pregnant women may also produce antibodies against fetal serum proteins if they display paternal allotypes (19, 32). One such reaction has even been associated with a unique form of hemolysis in the newborn (19).

Finally, pregnant women elaborate antibodies directed against placental antigens including trophoblast membranes, trophoblast basement membrane components and intracytoplasmic antigens of the syncytial trophoblast (16, 20, 24, 29). Some of these antibodies may have activities that spill over into the cellular immune system. For instance, Youtananukorn and Katangkasonbut (56) have shown that plasma factors reacting with placental antigens also have the capacity to inhibit macrophage migration. This inhibitory effect seems to be quite specific in that it did not inhibit responses to an unrelated antigen, in this case PPD, and was not present in nulliparous women or in men (56).

It appears, therefore, that as far as the humoral immune system is concerned, the pregnant woman is capable of responding normally to challenges from external agents (i.e., immunization) as well as from fetal antigens derived from the paternal contribution. The wide variety of responses noted above suggest that there is no lack of recognition or response despite the pregnant condition.

Cellular Immunity

The cellular arm of the immune system is likewise measured by enumerating its components as well as by determining its function in vivo and in vitro. There is some controversy about the numbers of circulating T and B cells during pregnancy. Two studies describe no change (7, 13), one an increase (12) and three a decrease (6, 18, 47) in circulating T lymphocytes during pregnancy. The most recent study (46) utilized monoclonal antibodies to study not only T and B cell numbers but T-helper and T-suppressor cell subsets as well. They found a significant decrease in the numbers of circulating T cells in the second and third trimesters. They suggested that they could account for this decrease in the total T cell population by a persistent decrease in the absolute number of T-helper cells which exists throughout pregnancy. Neither T-suppressor cells nor B cells varied in number during pregnancy. However, the percentage of monocytes did increase. Whether this decrease in T-helper cell numbers plays an important role in pregnancy immunology has yet to be determined.

T cell function, as measured by the blast transformation to mitogen stimulation has been found to be depressed during pregnancy (4, 40) and has also been found to be unchanged (3, 8). Similar controversy exists about the effect of pregnancy on the mixed lymphocyte culture response of the mother's lymphocytes in a one-way reaction (5, 9, 15, 39). Less confusion exists about the cytotoxicity that develops in maternal cells and is directed against cultured fetal cells (50, 52). Maternal cells have shown cytotoxicity toward fetal cells beginning at about the 14th week of gestation and continuing throughout pregnancy.

The in vitro correlates of a generalized depression of cell mediated (T cell) immunity have also been difficult to define. Lichtenstein (26) studied 82 female patients with tuberculosis who became pregnant. Intradermal skin testing demonstrated that not a single tuberculosis patient was completely insensitive to tuberculin during pregnancy. There was, however, a mild depression of sensitivity in the third trimester that was manifested as a decrease in the size of the reaction. In another study, BCG immunotherapy was used as a treatment for recurrent herpes genitalis in women (1). Three of these women became pregnant and they lost their skin test positivity in the second and third trimesters. Skin response reappeared about 12 weeks after parturition. Interestingly, skin test positivity also disappeared when one of those women was started on oral contraceptives as well.

Pregnancy-Associated Proteins

At this point, it is worthwhile to mention that a great deal of research has been performed to investigate the role of the pregnancy-associated proteins (PAP) and hormones in the generalized immunosuppression of the mother. These substances are elaborated by the trophoblast and have been thought to be important for the maintenance of a normal pregnancy. Certainly, increased levels of estradiol, progesterone and cortisol may have a variety of local and systemic effects including the suppression of immune reactivity (as measured by PHA stimulation), the increase of graft survival and the decrease of inflammatory activity. The exact role that each of these hormones plays is unclear and an understanding of their interrelationships has not yet been fully developed.

Human chorionic gonadotropin has received much attention as an immunosuppressive agent but recent investigations have cast doubts as to which protein actually has biological activity (30–31). The same must be said for α-fetoprotein (25). Other pregnancy-associated proteins that have been evaluated for their immunological activity include proteins of the A_2-globulin class (pregnancy zone protein, pregnancy-associated macroglobulin, pregnancy-associated globulin and pregnancy-associated plasma proteins A, B, and C), and the B_1-globulin class (pregnancy specific B globulin, and B_1 glycoprotein). Their structures have been reviewed (21) and other than to note that a variety of immunosuppressive effects on T cell function have been ascribed to them, particularly in isolated systems in vitro, they will not be considered further.

Current Theories

It would appear then, that generalized immunosuppression is not a part of the normal pregnancy. Most of the current evidence indicates that both the humoral and cell-mediated functions of the immune system are intact. The explanation presently in vogue for understanding the maintenance of pregnancy is that specific "blocking factors" are involved. These factors may be elaborated by the mother (for example: anti-HLA antibodies), they may be circulating immune complexes or they may be substances produced by fetal suppressor cells.

Anti-HLA antibodies have been shown to inhibit the mixed lymphocyte reaction (38), inhibit the production of migration inhibitory factor (43), and inhibit the cytotoxicity of maternal lymphocytes when cultured with human trophoblast (56). Maternal serum could block the reaction of both the stimulator cells (paternal or unrelated) and the responder cells (maternal) in one way mixed cell cultures (38). This activity could be removed by absorption with platelets or leukocytes suggesting HLA dependence; however, antibodies to other cell surface determinants might be equally as important. Interestingly, these sera had no effect on PHA response. Other studies have shown that maternal serum inhibits the production of migration inhibition factor when maternal lymphocytes are cultured with fetal (43) or paternal (37) lymphocytes. Although some doubt exists as to the specificity of the blocking antibodies, it is clear that their activity is reduced in the sera of women who habitually abort (42) and it is theoretically conceivable that this condition might be treated by judicious immunization with the appropriately HLA typed platelets or leukocytes.

The suggestion that immune complexes may play a role in the blocking activity of maternal serum stems from observations of tumor immunity (45). Whether or not circulating immune complexes exist during pregnancy is currently being disputed (reviewed in 51). However, the great variety of the biological effects of circulating immune complexes mediated through their binding to Fc and/or complement receptors make them a likely candidate for an important role in specific immunosuppression. It has certainly been demonstrated that the requisite antibodies, i.e, those directed against fetal (paternal) antigens, are formed. The size, nature, and activities of such complexes need further study. Solubilized complexes or idiotype anti-idiotype complexes may co-purify with immunoglobulin fractions and either might be responsible for the biological activity noted in the IgG fraction of serum.

The last type of specific suppressor activity to be considered is that activity generated by fetal suppressor cells. It is well established that fetal lymphocytes have the capacity to make a strong response in mixed lymphocyte cultures and to mitogenic stimulation (10, 11). However, when human cord lymphocytes were co-cultured with maternal lymphocytes in the presence of PHA, a marked but not complete suppression of maternal response could be demonstrated (33, 35). This suppressor activity is associated with the subpopulation we now call T-suppressor cells (36) and does not require cell-cell interaction. In fact, the suppressor factor(s) can effectively inhibit maternal lymphocyte proliferation even when the two cell populations are separated by a cell-impermeable membrane (34). Additional evidence comes from studies indicating that cultures of nonstimulated cord monocytes elaborate soluble factors that inhibit lymphocyte response to PHA, mixed leukocyte reactivity and production of leukocyte inhibitory factor (55). Thus, it would appear that the fetus may play an active role in preventing the maternal immune system from rejecting it.

Summary

This review has developed the following themes:

- The immune system of the mother is basically intact. Although the pregnant woman may suffer more severely from some types of viral infections (influenza pneumonia particularly), she is not at risk from more frequent or more severe infections from most viral or bacterial pathogens. One study has shown that approximately 5% of pregnancies are complicated by 1 viral infection, 0.4% by 2 viral infections, and 0.03% by more than 3 viral infections (44). In vivo tests of immunologic function i.e., immunization for humoral activity and maintenance of skin test reactivity for cell mediated immune function, also seem to be generally normal (17).
- Immunosuppression probably does play a role in the maintenance of a normal human pregnancy but it is likely to be quite specific, utilizing specific antibodies, immune complexes or lymphocytes, and/or quite localized, i.e., the development of reactive maternal cells is prevented in and around the placenta but not necessarily elsewhere in the mother.
- Clinically inconsequent, generalized immunosuppression may be detected by laboratory tests and has been ascribed to a variety of substances, factors, proteins, and hormones. A complete understanding of the interrelationship of all these complex physiologic processes awaits further research and a better grasp of the mechanisms of the functioning of the immune system.

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Endocrinology of Pregnancy

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Since the last edition of this text, reproductive endocrinology has undergone a significant reversal of emphasis. Investigative interest has shifted from documenting the source and effect of hormonal secretions on diverse target organs to an appreciation of the endocrine organ as a self-contained autoregulatory unit whose secretions sustain, modify, and enhance local function. Secretion of circulating messengers are increasingly viewed as internal signals for assistance in achieving maximally appropriate local paracrine function as much as impacting on distant organ activity. Perhaps nowhere in biology is this new concept more evident than in the endocrinology of pregnancy. Here endocrine mechanisms exist by which the evolving, maturing fetoplacental unit influences its environment to ensure adequate blood flow and nutrition to sustain organ differentiation and development. Indeed, evidence is now in hand to implicate the fetoplacental unit in signaling its readiness for extrauterine existence by initiating events leading to labor. This chapter will review the biochemistry and physiology of the steroid, peptide, and prostaglandin hormone "messengers" of pregnancy from this "new" point of view.

Steroid Hormones (94)

In the conventional view of steroid synthesis applicable to the adrenal cortex and the gonads, characteristic hormone synthesis and secretion unique to the organ are generated through a biosynthetic cascade contained entirely within the gland itself. The fetoplacental unit does not follow this rule. Here, the individual participating organ elements do not possess the necessary enzymatic capabilities to complete steroidogenesis. However, by an arrangement whereby one organ's attributes compensate for the deficiency of its partner, together synthesis of massive quantities of corticoids, progestins, androgens, and estrogens is achieved. Thus the "fetoplacental unit" is more than an anatomic designation; it is an interacting interdependent biochemical and physiologic entity as well. Table 1 and Fig. 1 review the distribution of synthetic properties within the unit. The maternal "compartment" is at once a source of precursor, a metabolic clearinghouse and a target organ for fetomaternal secretions.

Progesterone. The massive amounts of progesterone produced in human pregnancy reflects placental-maternal cooperation (Figs. 2, 3) (21, 74). In the first 6 weeks of gestation, human chorionic gonadotropin (hCG) stimulation of the corpus luteum induces secretion of approximately 25 mg of progesterone a day. During this period of pregnancy, levels of 17α-hydroxyprogesterone also increase, marking the activity of the corpus luteum as the major source of both steroids (placenta has no 17α-hydroxylase capacity at this stage). Progesterone concentrations remain at the postovulatory corpus luteum phase levels in this interval (Fig. 4). By the 10th week, 17α-hydroxyprogesterone returns to baseline levels while progesterone secretion from the placenta emerges as the sole source of this hormone and progesterone levels rise.

During the transition period between 6 and 10 weeks in which both the placenta and corpus luteum contribute to total progesterone production, hemorrhagic accidents, and/or surgical ablation of the corpus luteum require hormone replacement support of the early pregnancy. Thereafter, progesterone synthesis within the placenta is self-sustaining: at 3 months' gestation, levels of production begin to rise linearly so that at term (36–40 weeks) progesterone concentrations range

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TABLE 1

Distribution of Steroid Biosynthetic Enzymes within the Fetoplacental Unit

Biosynthetic step	Placenta	Fetus
Acetate → cholesterol	–	+
Cholesterol 20–22-hydroxylase	+	+
17α-Hydroxylase	–	+
3β-ol-Dehydrogenase	+	–
17–20-Desmolase	–	+
Aromatase	+	+
16α-Hydroxylase	–	+
Sulfokinase	+	+
Sulfatase	+	–

from 100 to 200 mg/ml and secretion by the placenta reaches 250 mg per day.

As can be seen in Fig. 3, placental progesterone is derived from maternal cholesterol. In contrast to fetoplacental estrogen production, progesterone is made available, independent of uteroplacental perfusion, fetal well-being, or even a live fetus. Maternal cholesterol is provided by LDL-cholesterol transferred to the trophoblast by endocytosis involving LDL-specific membrane receptors (91). By this process, cholesterol is made available for biosynthesis, lysosomal breakdown of LDL liberates amino acids for local or fetal transfer, and hydrolysis of cholesterol ester yields essential fatty acids for similar disposal.

Where does all this progesterone go and what does it do (Table 2)? Obviously, a large quantity enters the *maternal compartment.* Elsewhere in this chapter, the role of progesterone in the initiation of labor will be examined in detail; at this point, it is sufficient to note that myometrial levels are about 3 times higher than maternal plasma concentrations in early pregnancy and remain high for the rest of the pregnancy.

Progesterone metabolism in the maternal compartment may have physiologic significance. 5α-Reductase action yields a pregnane derivative (pregnanolone) which contributes to insensitivity to the pressor action of angiotensin II. Desoxycorticosterone (DOC) is the 21-hydroxylated metabolite of progesterone. Its concentration in maternal blood at term is 1200 times higher than nonpregnant levels (75). Only a small portion of this elevation is due to increased cortisol binding globulin capacity (estrogen induced). The majority is the result of 21-hydroxylation of progesterone in the maternal kidney. The importance of these progesterone derivatives in altering maternal fluid volume and blood pressure are highly suggestive but remain to be characterized in health and disease. Finally, progesterone may be important in suppressing the maternal immunological response to fetal antigens, thereby preventing maternal rejection of the trophoblast (89).

Progesterone secretion is also directed to the *fetal* side. Amniotic fluid progesterone concentration is maximal between 10 and 20 weeks but then gradually decreases. Progesterone serves the important role of precursor substrate for fetal adrenal cortex glucocorticoid and mineralocorticoid synthesis and bioavailability. As has been noted, the fetal adrenal has no 3β-ol-dehydrogenase and isomerase activity. It is therefore an active source of sulfated dehydroepiandrosterone and other Δ^5-3β-ol-steroids. The fetus must borrow progesterone as the Δ^4-3-ketone precursor for hydroxylation to cortisol, DOC, and aldosterone. Maternal corticoids do not survive placental passage in biologically active form.

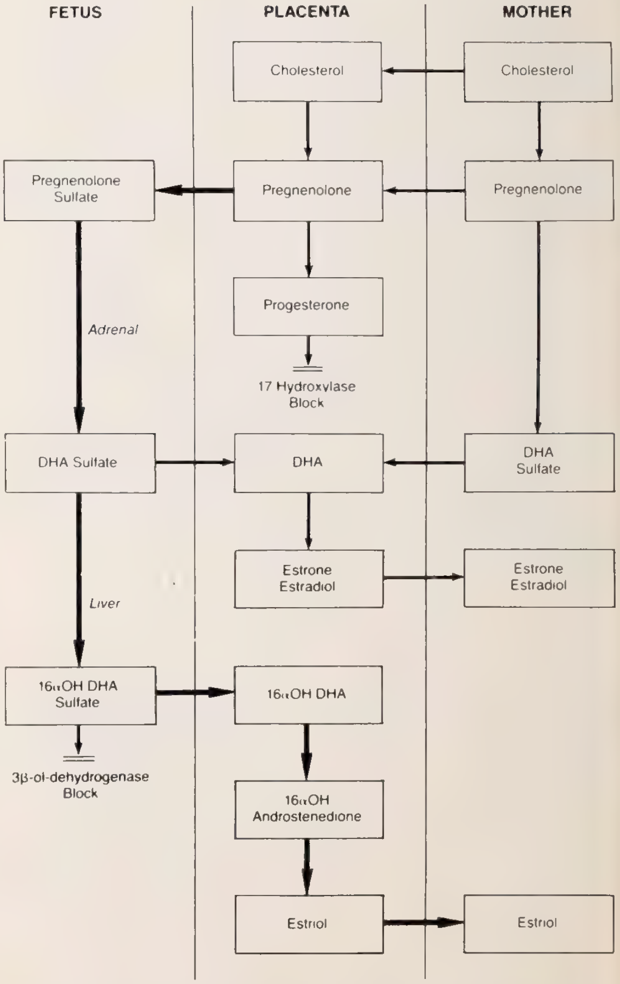

Fig. 1. Composite steroid biosynthetic mechanism within fetoplacental-maternal unit. Note interdependence of fetal, placental, and maternal processes (specified in Table 1) leading to characteristic steroid secretions (94).

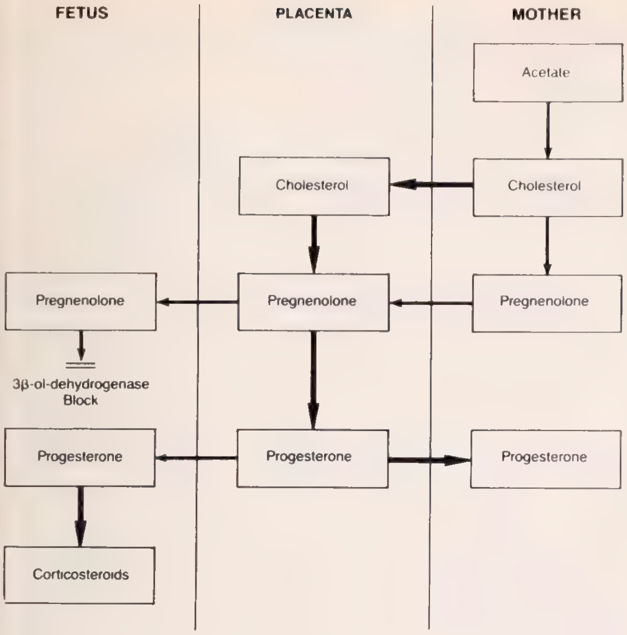

Fig. 2. **Left** Composite diagram of progesterone synthesis in fetoplacental-maternal unit. Beyond 8–10 weeks, primary site of synthesis and secretion is placenta. In fetus, it is utilized as precursor for corticoid synthesis in fetal adrenal (94).

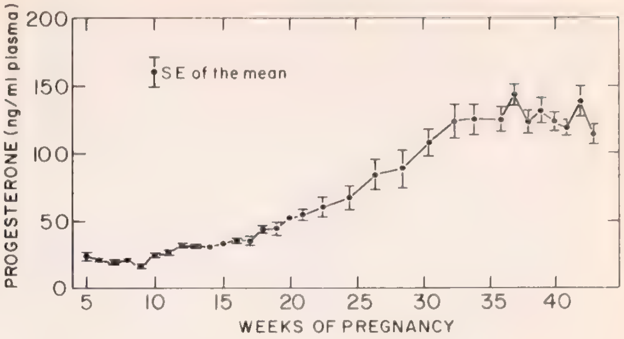

Fig. 3. **Above** Plasma progesterone concentrations in maternal peripheral venous blood throughout pregnancy. Note relatively stable levels in first 10–12 weeks, a rapid increase in second trimester, and a final plateau in last 10 weeks to term.

Estrogens. More than 25 different estrogens have been isolated from the urine of pregnant women. Most are maternal and fetal conjugates or metabolites of hormones secreted by the placenta. The three classic estrogens (estrone, E_1; estradiol, E_2; and estriol, E_3) are the three estrogens secreted by the placenta that have been studied extensively (10, 11).

The maternal plasma concentrations of the unconjugated forms of these estrogens throughout pregnancy are depicted in Fig. 5. Although individual variation in E_1 and E_2 is considerable precluding application to fetal monitoring, serial E_3 concentrations are steep, progessive, and reasonably limited in day-to-day variability. Urinary excretion of E_1 and E_2 is increased 100 times in pregnancy; for E_3, the increment is 1000 fold. It will be seen that the bulk of E_3 in pregnancy is fetal in origin.

The basic precursors of estrogens are 19 carbon androgens (Fig. 1) (76). However, the source of these androgens is not placental where there is a virtual absence of 17-hydroxylation and 17-20-desmolase activity in that organ. As a result, progesterone and pregnenolone cannot be converted to androgen here. Like progesterone, estrogen produced by the placenta must be elaborated from precursors outside the placenta; but unlike progesterone, estrogen precursors come from the *fetus*. By the 20th week of pregnancy, the vast majority of estrogen appearing in maternal blood and urine is derived from fetal androgens. In particular, approximately 90% of excreted estriol can be accounted for by dehydroepiandrosterone sulfate (DS) production by the fetal adrenal gland. The fetal adrenals secrete more than 200 mg of DS daily, fully 10 times greater than the mother. In a pregnancy with an anencephalic fetus, the absence of fetal adrenal function is demonstrated by extremely *low* maternal blood and urinary estrogen levels. DS is transferred to the placenta or

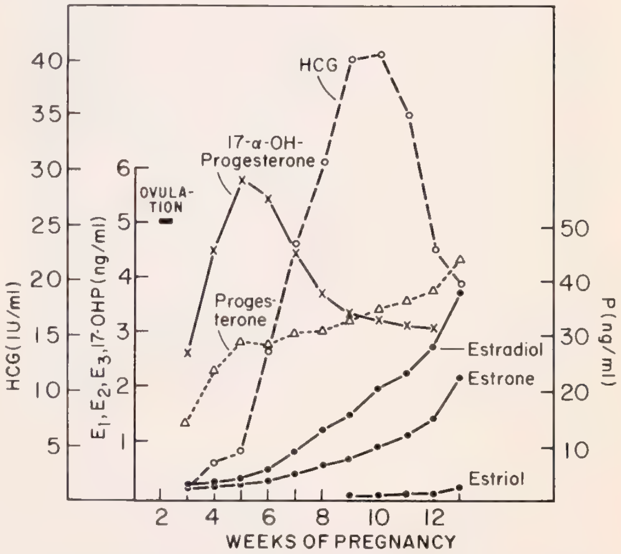

Fig. 4. Detailed plot of maternal concentrations of human chorionic gonadotropin (HCG), progesterone, 17αOH-progesterone, and the three estrogens (estradiol, estrone, and estriol) in the first trimester. Note fall in 17αOH-progesterone as corpus luteum diminishes in steroid secretion. Distribution of 17α-hydroxylase thereby provides useful marker for corpus luteum (+) and placental (−) contribution to overall progesterone production.

TABLE 2

Possible Functions of Progesterone in Pregnancy

Maternal
1. Maintain myometrial quiescence
2. Counterbalance fluid and salt retention secondary to aldosterone
    a. Direct natriuretic effect
    b. Formation of pregnanolone
3. Conversion to desoxycorticosterone in maternal kidney; a further influence on salt content and fluid volume control
4. Enhancement of immunologic acceptance of fetus
5. Influence insulin secretion and insulin activity

Fetal
1. Precursor source for synthesis of
    a. Cortisol
    b. Desoxycorticosterone
    c. Aldosterone
2. Antiandrogen
3. Antiestrogen

first converted to a 16α-hydroxy-DS in the fetal liver (the placenta also lacks this hydroxylase). Once in the placental compartment, DS and 16-hydroxy-DS are sulfatased, converted to corresponding androgens and aromatized to estrogens (Fig. 1).

The purpose of the large quantities of estrogen circulating in pregnancy is not entirely understood (Table 3). On the fetal side, estrogen may account for the massive growth of the fetal adrenal cortex during gestation, the characteristic disproportionate development of the inner fetal cortex (85% of the gland), and its biochemical inability to convert 3β-ol-Δ^5-steroids to the Δ^4-3-ketone type. Presumably early in pregnancy, the fetal adrenal responds to hCG, but soon fetal ACTH is required. Prolactin does not stimulate fetal adrenal cortex growth or function.

Estrogen on the maternal side may control blood flow to the uterus by effecting hepatocyte production of renin substrate (angiotensinogen) as well as enhancing prostaglandin (PG) synthetase function locally and generally. These complex issues will be reviewed in more detail subsequently in this chapter.

Peptide Hormones (94)

Human Chorionic Gonadotropin. Human chorionic gonadotropin (hCG) is a glycoprotein, a peptide framework, to which carbohydrate sidechains are attached. Alterations in the carbohydrate components (about one-third of the molecular weight) may alter biologic properties. For example, the half-life of hCG is approximately 24 hours as compared to 2 hours for LH, a 10-fold difference which is due mainly to the greater sialic acid content of hCG. As with the other glycoproteins, FSH, LH, and TSH, hCG consists of two noncovalently linked subunits, called alpha (α) and beta (β). The α subunits in these glycoprotein hormones are virtually identical, consisting of 89 to 92 amino acids. Unique biological activity as well as specificity in radioimmunoassays is attributed to the molecular differences in the β subunits.

The 30 terminal amino acids of β-hCG are different from the sequence of LH. Despite this difference (which allows specific antisera to discriminate between hCG and LH in assays), hCG is biologically similar to LH. As such, hCG supports the corpus luteum, taking over for LH on about the 8th day after ovulation when β-hCG can be detected in maternal blood for the first time.

Also because of its LH-like activity, hCG stimulates steroidogenesis in the Leydig cells of the early fetal testes. This androgen production initiates the masculine differentiation that will be sustained and enhanced as fetal pituitary LH appears (50). It also appears that the function of the inner fetal zone of the adrenal cortex may depend upon hCG for steroidogenesis early in pregnancy. hCG may also be necessary for placental steroidogenesis.

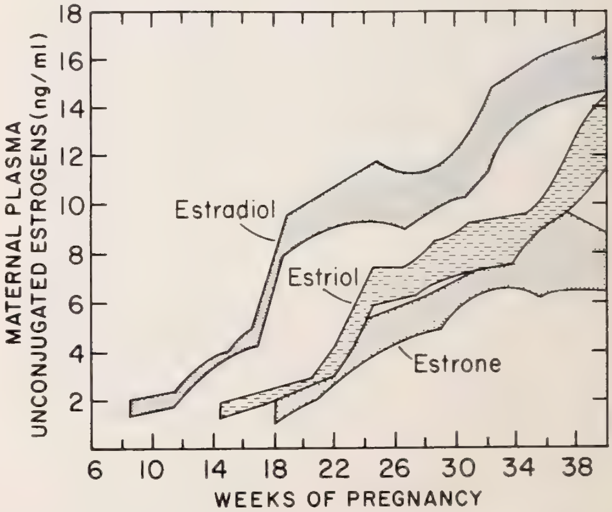

Fig. 5. Maternal plasma concentrations of *unconjugated* estrogens (estradiol [E_2], estrone [E_1], estriol [E_3]) throughout pregnancy. As noted in Figure 1, whereas E_1 and E_2 are "mixed" in origin, E_3 reflects uniquely fetal activity (16-hydroxylation).

TABLE 3

Possible Functions of Estrogen in Pregnancy

Maternal
1. Control of blood flow to uterus and uteroplacental perfusion by
    a. Inducing angiotensinogen synthesis
    b. Increasing prostaglandin synthesis
2. Yielding prostacyclin and prostaglandin E_2 local and general vasodilation
    a. combined increased circulating volume and balanced blood pressure
3. Stimulatory effects on reproductive target organs, i.e. breasts, uterus, cervix, vagina

Fetal
1. Female differentiation
2. Fetal adrenal zone hypertrophy and hyperplasia
3. Induction of 3β-ol-dehydrogenase block

hCG is secreted by the syncytiotrophoblast, its concentrations reaching a maximum level of 50,000 to 100,000 mIU/ml at 10 weeks' gestation. The old bioassay tests for pregnancy have been replaced by immunological and receptor tests for the presence of hCG in maternal blood and urine. These new tests are reliable with essentially no false positive reactions. False negative results may occur prior to the 5th or 6th week of gestation because the sensitivity threshold of the tests must be maintained at a level high enough to avoid cross-reactions with LH.

hCG levels decrease to about 10,000–20,000 mIU/ml by 20 weeks and remain at that level to term. hCG levels close to term are higher in women bearing female fetuses (6, 107). This is true of serum levels, placental content, urinary levels, and amniotic fluid concentrations. The mechanism and purpose of this difference are not known.

Two clinical conditions in which blood hCG titers are very helpful are trophoblastic disease and ectopic pregnancies. In the follow-up of terminated molar pregnancies, in patients without persistent disease, the hCG titer should fall to a nondetectable level by 1.5 weeks. Patients with trophoblastic disease show an abnormal curve (a titer greater than 500 mIU/ml) frequently by 3 weeks and usually by 6 weeks (87).

Virtually 100% of patients suspected of an ectopic pregnancy, but not having the condition, will have a negative blood hCG assay (88). A positive test can also be utilized in diagnosis. The hCG level increases at different rates in normal and ectopic pregnancies. In a normal pregnancy, the hCG should approximately double every 2 days (46). An hCG above 6000 mIU/ml is almost always associated with an intrauterine pregnancy. When the hCG titer is below 6000 mIU/ml and ultrasound examination fails to identify an intrauterine pregnancy, a patient may be managed expectantly if the hCG titer doubles in 2 days (47). If the titer does not double, laparoscopy is indicated. Laparoscopy is also indicated when the titer is above 6000 mIU/ml and ultrasound shows no evidence of an intrauterine pregnancy.

Human Placental Lactogen. Human placental lactogen (HPL), also secreted by the syncytiotrophoblast, is a single chain complexly curved polypeptide stabilized in configuration by two disulfide bonds. Although its amino acid constitution is 96% similar to human growth hormone (HGH), HPL has only 3% of HGH somatotropin activity. Although HPL has about 50% of the lactogenic activity of sheep prolactin in certain bioassays, maternal prolactin is the dominant factor in breast preparation during human pregnancy. The level of HPL in the maternal circulation is correlated with fetal and placental weight, plateauing in the last 4 weeks of pregnancy (Fig. 6). There is no circadian variation, and only minute amounts of HPL enter the fetal circulation. Very high maternal levels are found in association with multiple gestations; levels up to 40 μg/ml have been found with quadruplets and quintuplets. Anything less than 4 μg/ml is an abnormally low level in the last trimester.

Experimentally, the maternal level of HPL can be altered by changing the circulating level of glucose. HPL is elevated with hypoglycemia and depressed with hyperglycemia. This information, combined with studies in fasted pregnant women, offers strong evidence that HPL participates in regulating maternal fuel utilization and transfer to the fetus (see below) (27, 92).

Human Chorionic Thyrotropin. The human placenta contains two thyrotropic substances. One is called human chorionic thyrotropin (HCT) and is similar in size and action to pituitary TSH. Its content in the normal placenta is very small. HCT differs from the other glycoproteins in that it does not appear to share the common α subunit. Antiserum generated to α-hCG does not neutralize the biologic activities of HCT, but it does that of HCG and pituitary TSH. Rarely, patients with trophoblastic disease may also display hyperthyroidism. Studies indicate that hCG has intrinsic thyrotropic activity, and thus represents the second placental thyrotropic substance (68).

On a molecular basis, it is calculated that hCG contains approximately 1/4000th of the thyrotropic activity of human TSH (52). In conditions with very elevated hCG levels, the thyrotropic activity can be sufficient to produce hyperthyroidism. Receptors for TSH may react to hCG as an example of a "spill over" reaction to the massive excess of a not quite alien glycoprotein.

Human Chorionic Adrenocorticotropic Hormone (HCACTH). There is evidence that the rise in free cortisol which takes place throughout pregnancy may be due to ACTH production by the placenta (83). The placental content of ACTH is higher than can be accounted for by the contribution of sequestered blood. In addition, cortisol levels in pregnant women are resistant to dexamethasone suppression, suggesting there is a component of maternal ACTH which does not originate in the maternal pituitary gland. These observations have stimulated speculation that placental ACTH raises maternal adrenal activity in order to ensure provision of the basic building blocks (cholesterol and pregnenolone) for placental steroidogenesis.

Other Placental Peptides. β-Endorphin and β-lipotropin are synthesized in the human placenta. In addition, both fetal and maternal blood levels of β-endorphin increase during labor, probably originating from the respective pituitary gland and secreted in parallel with ACTH (39). Fetal levels at delivery are higher than adult levels, and are inversely correlated with arterial pH and Po_2 (104). Whether measurement of this peptide can be utilized clinically remains to be determined.

The human placenta contains a number of releasing and inhibiting hormones, including GnRH, TRH, and somatostatin (90). Immunoreactive GnRH can be localized in the cytrotrophoblast.

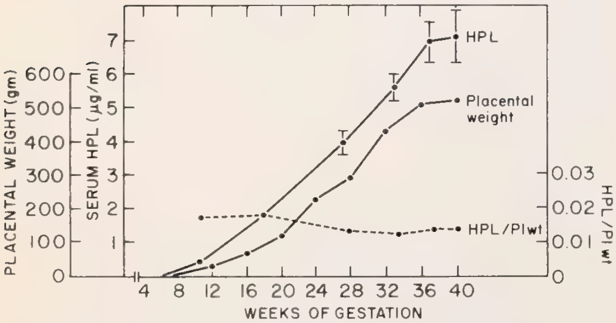

Fig. 6. Human placental lactogen (HPL) concentration in maternal serum correlates with placental weight throughout pregnancy.

Several investigators (66, 70) have suggested that the control of synthesis and release of hormones such as HPL, hCG, HCACTH, β-lipotropin, and β-endorphin are controlled by releasing factors found in the cytotrophoblast (gonadotropin releasing hormone, GnRH, and corticotropin releasing hormone, CRF). In these formulations, the releasing factor from the cytotrophoblast stimulates RNA synthesis and secretion of the specific peptide from the syncytiotrophoblast (Fig. 7).

The trophoblast secretes a pregnancy-specific β_1-globulin into the maternal secretion. It appears shortly after implantation and increases steadily until term. Its functions and importance are unknown, but it is already saddled with a difficult name, Schwangerschafts protein 1 (SP_1). The placenta pours a flood of proteins into the maternal circulation, and it remains to be seen whether their identity and function can be sorted out.

α-Fetoprotein. α-Fetoprotein (AFP) is a relatively unique glycoprotein derived largely from fetal liver, and partially from the yolk sac until it degenerates at about 12 weeks. In fetal blood it may serve as a protein carrier of estrogen thereby preventing feminization of male fetuses. Peak levels are reached early in the second trimester (16–18 weeks), then decrease gradually until term. Because AFP is concentrated in the central nervous system (CNS), exposure of CNS to the amniotic fluid (as with neural tube defects) results in elevated amniotic fluid and maternal blood levels. Other fetal abnormalities, such as intestinal obstruction, omphalocele, and congenital nephrosis, are also associated with high levels of AFP in the amniotic fluid. Maternal blood levels of AFP reflect the amniotic fluid level. Because of a high incidence of false positive results in maternal serum AFP screening programs, each patient with a high blood level requires ultrasound evaluation to detect multiple gestation, erroneous dating, or intrauterine demise. Only then is it necessary to do amniocentesis to measure the amniotic fluid AFP.

Relaxin. Relaxin is a peptide hormone produced by the corpus luteum of pregnancy, and not detected in men or nonpregnant women. While it has been argued that the human corpus luteum is the sole source of relaxin in pregnancy, it has also been identified in human placenta (28, 105). The maternal serum concentration rises during

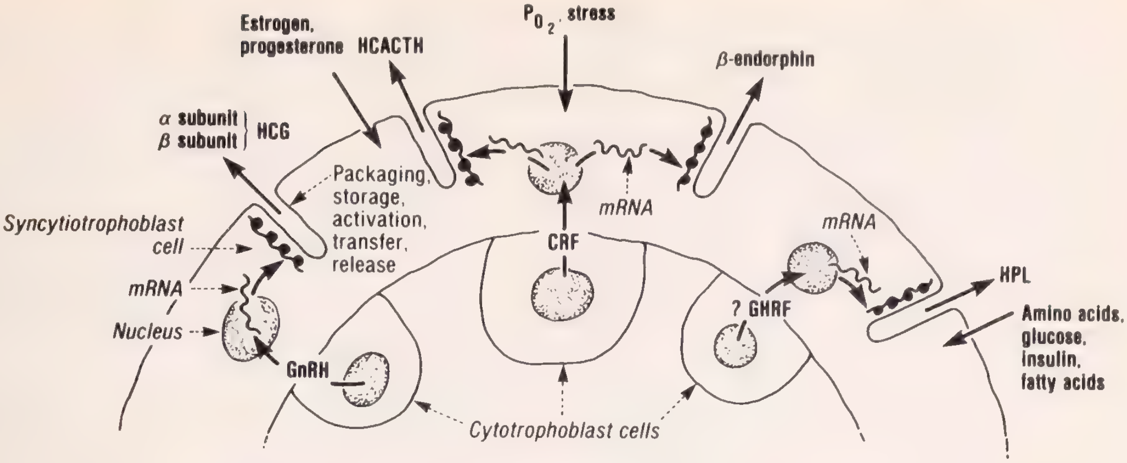

Fig. 7. Schematic representation of control of synthesis and secretion of human chorionic gonadotropin (HCG), human chorionic adrenocorticotropic hormone (HCACTH), β-endorphin, and human placental lactogen (HPL) in placenta. Theoretical linkages between releasing hormones and "feedback" signals may be basis by which cytotrophoblast directs syncytiotrophoblast synthesis, storage, transfer to secretory pools, and exocytosis.

the first trimester and declines in the second trimester (81). This suggests a role in maintaining early pregnancy, but its function remains to be established. In animals, relaxin softens the cervix, inhibits uterine contractions, and relaxes the pubic symphysis.

Prolactin. The decidualized endometrium of pregnancy appears to have a specialized endocrine function, the secretion of prolactin. Prolactin is synthesized by endometrium during a normal menstrual cycle, but this synthesis is not initiated until histologic decidualization begins (58). During pregnancy, prolactin secretion occurs only in the fetal pituitary, the maternal pituitary, and the uterus. Neither trophoblast or fetal membranes synthesize prolactin, but both the myometrium and endometrium can produce prolactin (5, 103). Prolactin production by the myometrium is unaffected by its hormonal environment, but the endometrium requires the presence of progesterone to initiate prolactin synthesis, while progesterone suppresses synthesis in the myometrium. Prolactin derived from the decidua, therefore, is the source of the prolactin found in the amniotic fluid (85).

The maternal and fetal blood levels of prolactin are derived from the respective pituitary glands. Bromocriptine suppression of pituitary secretion of prolactin throughout pregnancy produces minimal maternal and fetal blood levels, yet there is normal fetal growth and development, and amniotic fluid levels are unchanged (43). Curiously, decidual secretion of prolactin is unaffected by bromocriptine.

Decidual prolactin may be important for fluid and electrolyte regulation of the amniotic fluid. Although no clinical significance can be attached to maternal and fetal blood levels of prolactin in abnormal pregnancies, decidual and amniotic fluid prolactin levels are lower in hypertensive pregnancies and in patients with polyhydramnios (55). Prolactin receptors are present in the chorion laeve, and their concentration is lower in patients with polyhydramnios (41).

Prostaglandins

Biosynthesis. The family of prostaglandins with the greatest biologic activity is that having two double bonds, being derived from arachidonic acid (82). Arachidonic acid can be obtained from two separate sources: directly from the diet (from meats) or by formation from its precursor linoleic acid which is found in vegetables. In the plasma 1–2% of the total free fatty acid content is free arachidonic acid. The majority of arachidonic acid is covalently bound in esterified form as a significant proportion of the fatty acids in phospholipids and esterified cholesterol. Arachidonic acid is only a minor fatty acid in the triglycerides packaged in adipose tissue.

The rate-limiting step in the formation of the prostaglandin family is the release of free arachidonic acid (Fig. 8). A variety of hydrolases may be involved in arachidonic acid release, but because of the abundance of arachidonate in the 2 position of phospholipids, phospholipase A_2 activation is an important initiator of prostaglandin synthesis. Types of stimuli that activate such lipases include: burns, infusions of hyper- and hypotonic solutions, thrombi and small particles, endotoxin, snake venom, mechanical stretching, catecholamines, bradykinin, angiotensin, and the sex steroids.

After the release of arachidonic acid, the synthetic path can go in two different directions: the lipoxygenase pathway or the cyclooxygenase pathway (82). The 5-lipoxygenase pathway has several leukotriene products, now designated LTA_4, LTB_4, LTC_4, LTD_4, and LTE_4. The leukotrienes are synthesized as a consequence of an anaphylactic challenge and are considered to be major agonists in producing bronchospasm during an asthmatic attack. Leukotrienes are 100–1000 times more potent than histamine or prostaglandins on the pulmonic airway. They stimulate an immediate vasoconstriction followed by leakage of fluid. Further roles are postulated for a variety of inflammatory responses, including arthritis.

The 12-lipoxygenase pathway leads to 12 hydroxyeicosatetraenoic acid (HETE). Little is known about 12-HETE other than that it is a leukostatic agent. The lipoxygenase products can also release lysosomal proteolytic enzymes.

The first true prostaglandin compounds formed are PGG_2 and PGH_2 (half-life of about 5 min), the proximal precursors of all other prostaglandins. The numerical subscript refers to the number of double bonds. This number depends on which of the three precursor fatty acids has been utilized. Besides arachidonic acid, the other two precursor fatty acids are linoleic acid, which gives rise to the PGG_1 series, and pentanoic acid, the PGG_3 series. The arachidonic acid family is the only one with physiologic importance. The prostaglandins of original and continuing relevance to reproduction are PGE_2, $PGF_{2\alpha}$, and possibly PGD_2. The A, B, and C prostaglandins either have little biological activity, or do not exist in significant concentrations in biological tissues.

Thromboxane and Prostacyclin. Thromboxanes are not true prostaglandins due to the absence of the pentane ring, but prostacyclin (PGI_2) is a legitimate prostaglandin. Thromboxane (TXA_2, half-life about 30 sec) and PGI_2 (half-life about 2–3 min) each have powerful biologic activities which balances the other. TXA_2 is the most powerful vasoconstrictor known, while PGI_2 is a potent vasodilator. These two agents also have opposing effects on platelet function (Fig. 9). Platelets and spleen predominantly synthesize TXA_2, while the heart, stomach, and blood vessels throughout the body synthesize PGI_2. The lungs are a major source of both agents. Normal pulmonary endothelium makes prostacyclin while TXA_2 appears in response to pathological stimuli (40). The pulmonary release of prostacyclin may contribute to the body's defense against platelet aggregation (62).

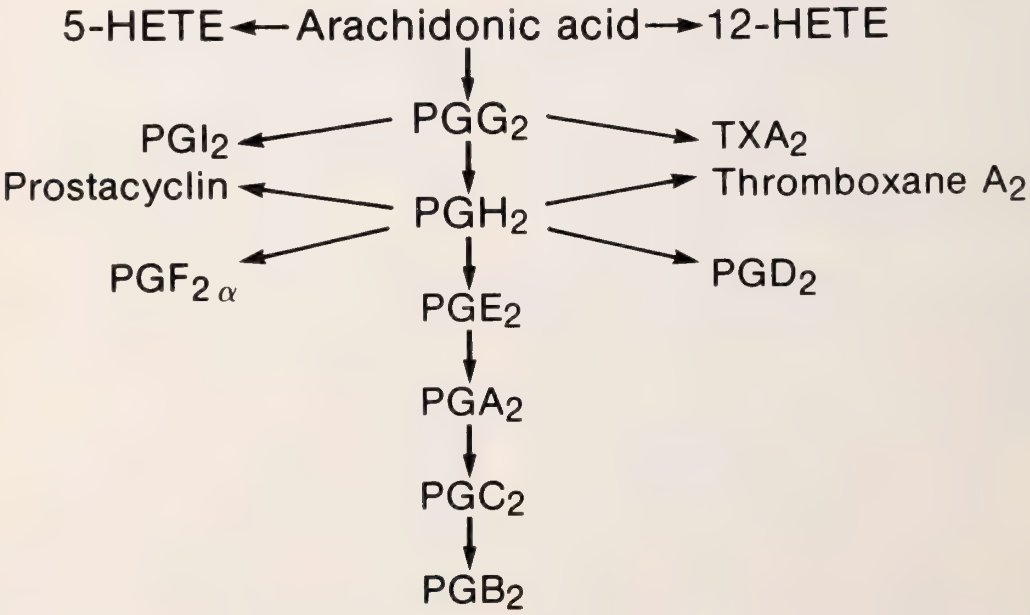

Fig. 8. The biosynthesis of prostaglandins, including the lypoxygenase and cyclooxygenase precursors. HETE = hydroxyeicosatetraenoic acid, PG = prostaglandin, TX = thromboxane.

There is some controversy over whether prostacyclin circulates as a true hormone. Measured by indirect means (bioassay technique), prostacyclin appears to undergo about 50% inactivation in one circulation through peripheral tissue (63, 65). Direct measurement (gas chromatography), on the other hand, failed to detect prostacyclin in blood samples coming directly from pulmonary arteries and veins (16).

Platelet function reflects the biologic opposition of TXA_2 and prostacyclin. The primary function of platelets is the preservation of the vascular system. Blood platelets stick to foreign surfaces or other tissues. This process is called adhesion. They also stick to each other and form clumps; this process is called aggregation. Because platelets synthesize TXA_2, a potent stimulator of platelet aggregation, the natural tendency of platelets is to clump and plug defects in damaged vessel surfaces. The endothelium, on the other hand, produces PGI_2, and its constant presence inhibits platelet aggregation and adherences, keeping blood vessels free of platelet clumps, and ultimately clots. Thus, prostacyclin plays a defensive role in the body. It is four to eight times more potent a vasodilator than the E prostaglandins, and it prevents the adherence of platelets to healthy vascular endothelium. However, when the endothelium is damaged, platelets gather, beginning the process of thrombus formation. Even in this abnormal situation, increased PGL_2 can be measured in injured endothelium, thrombosed vessels, and in the vascular tissues of hypertensive animals apparently in a vain corrective effort.

Conditions associated with vascular disease may be understood through the prostacyclin-thromboxane mechanism (63, 64, 69, 110). For example, atheromatous plaques and nicotine inhibit prostacyclin synthesis. Increasing the cholesterol content of human platelets increases the sensitivity to stimuli which causes platelet aggregation due to increased thromboxane production (98). The well-known associations between low-density and high-density lipoproteins and cardiovascular disease may also be explained in terms of PGI_2. LDL inhibits prostaglandin production and HDL overcomes the LDL inhibition (69). Platelets from diabetics make more TXA_2. Platelets from Class A diabetic pregnant women make more TXA_2 than platelets from normal pregnant women. Platelets in women using oral contraceptives make more TXA_2 than controls. The same is true of smokers and individuals with strong family histories of cardiovascular disease.

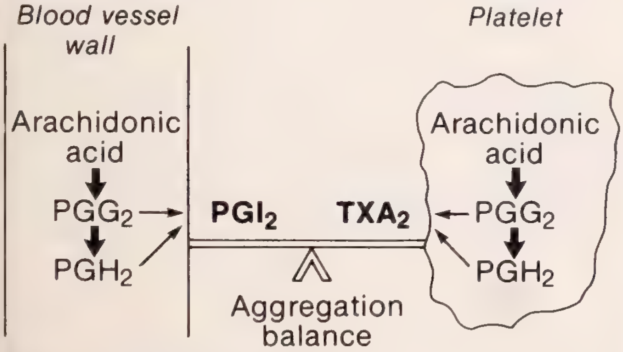

Fig. 9. Prostacyclin and thromboxane can be viewed as balancing elements at endothelial surface. Their opposing effects on vasoconstriction and platelet aggregation combine to maintain blood flow and endothelial surface integrity (94). PG, prostaglandin; TX, thromboxane.

Metabolism. The metabolism of prostaglandins occurs primarily in the lungs, kidney, and liver. The lungs are important in the metabolism of E and F prostaglandins. Indeed, there is an active transport mechanism which specifically carries E and F prostaglandins from the circulation into the lungs. Therefore, members of the prostaglandin family have a short half-life, and in most instances, exert their action at the site of their synthesis. Because of the rapid half-lives, studies are often carried out by measuring the inactive end products, for example 6-keto-$PGF_{1\alpha}$, the metabolite of prostacyclin, and TXB_2, the metabolite of thromboxane A_2.

Clinical Implications of Fetoplacental Endocrinology

Genesis of Sexual Dimorphism (51). During embryogenesis, the ovary can be distinguished from a testis by about the 6th week, but only by a process of exclusion, for morphologic differentiation of the ovary does not occur until later. At this early stage, both the structure and function of the temporarily dormant ovary contrast markedly with that of the testis. As shown in Fig. 10, by the end of the first trimester, the serum testosterone concentration in male fetuses has risen remarkably, achieving *adult male levels,* whereas that of the female appropriately remains at the basal level. Most authorities concur that the principal hormonal stimulus for embryonic testicular differentiation and subsequent testosterone secretion is the LH-like activity of hCG, which reaches its highest concentration in the fetal compartment coincident with the peak in fetal testicular testosterone secretion. Clearly, endocrine sexual dimorphism exists in the fetus even before significant morphological differentiation of the ovary, and interestingly, it is the specific testicular response to the ubiquitous hCG, present in equal concentrations in both male and female fetuses, that initiates this dimorphism. It has thus far been impossible to distinguish in human fetal serum between estradiol of fetal ovarian origin and that deriving from the placenta, but the concentration of estradiol in both male and female fetuses appears to be high (~5 ng/ml) and similar throughout human pregnancy. Although capable of aromatizing androgen in vitro at this early stage in embryogenesis, the fetal ovary in vivo either remains endocrinologically quiescent or contributes so little estradiol to the fetal pool that its steroidogenic activity is obscured by that of the placenta (Fig. 11).

By the beginning of the middle trimester, the ovaries have received an endowment of 6–7 million germ cells as the result of their early migration from the yolk sac and subsequent mitosis. At this stage, a second form of endocrinologic sexual dimorphism ensues—a clear divergence in fetal serum gonadotropin concentrations between the two sexes. In the middle trimester, the concentrations of both FSH and LH are higher in the female than in the male fetus. The difference is especially prominent for FSH (Fig. 12). Interestingly, the high concentration of estradiol in the fetal compartment at this time, 50 times that during a normal menstrual cycle, is unable to suppress release of FSH from the female fetal pituitary, an observation signifying an immature estrogen-gonadotropin negative feedback system. In contrast, FSH concentration in the male fetus is only 1/20th that of the female, presumably as the result of a potent negative feedback effect of testosterone and/or inhibin. At any rate, this marked sexual difference in gonadotropin concentrations stems ultimately from the early differences in response of the respective embryonic gonads to hCG.

The surge of fetal pituitary gonadotropin activity (predominately FSH) in serum of the female fetus at midpregnancy has a profound effect on ovarian differentiation. Concurrent with these stimuli, the oogonia advance to oocytes, enter the first meiotic division, and arrest in prophase (Fig. 13). Varying degrees of follicular maturation and atresia ensue. By this process, fully 80% of the initial germ cell population is depleted before birth, such that the total ovarian content of germ cells in the neonate is about 1–2 million.

Central Metabolic Role of Placenta in Normal Pregnancy (42). During gestation, the maternal endocrine-metabolic environment must change rapidly to accommodate a rapidly growing "tissue transplant," the fetus. The placenta plays a central role in both the delivery and modulation of maternal fuels to the fetus. During the first half of pregnancy, maternal carbohydrate metabolism is modified by a rise in serum levels of estrogen and progesterone (Table 4). Pancreatic β cell hyperplasia occurs, and there is an increase in in-

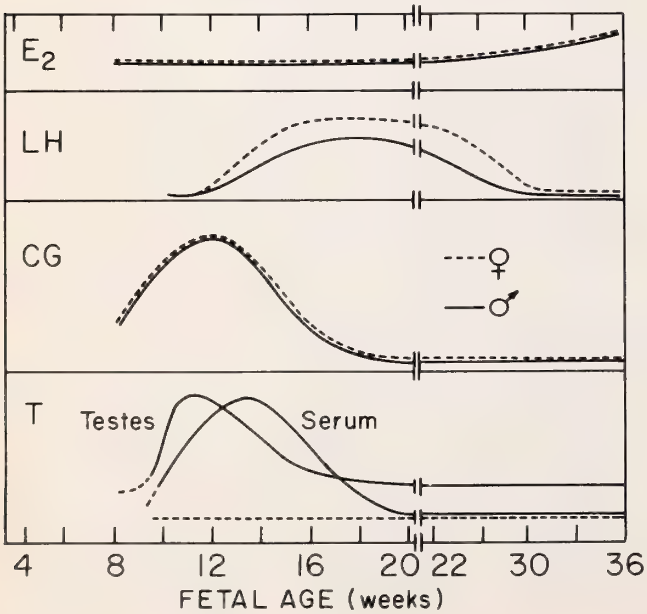

Fig. 10. Fetal hormones during early pregnancy. Note testosterone levels in male fetus are high in early gestation, originate in fetal testes, are initially stimulated by hCG, and are sustained by fetal pituitary LH (50).

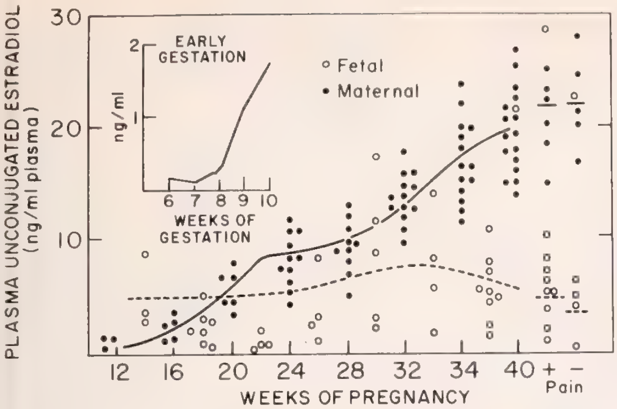

Fig. 11. Estradiol production by fetal ovary may occur, but unlike testicular synthesis of testosterone, female gonad estrogen contribution must be small, its activity obscured by placental function.

sulin secretion (18, 48). Hyperinsulinemia leads to an increase in peripheral glucose utilization, a decline in fasting plasma glucose levels, increased tissue storage of glycogen, and decreased hepatic glucose production.

As pregnancy progresses, the major physiologic challenge is to ensure transfer of an adequate supply of nutrients to a constantly feeding fetus from an intermittently fasting and feeding mother. Freinkel (30) was the first to describe these maternal metabolic changes of late pregnancy as "accelerated starvation" when food is unavailable and "facilitated anabolism" with food ingestion. Maternal fuel adjustments during late pregnancy include a sparing of maternal glucose utilization with decreased maternal levels of glucose and amino acids, a shift to an increased production of fatty acids and ketones, and pancreatic islet cell hypertrophy with an increased insulin response to glucose. Table 5 shows hormonal changes associated with pregnancy, their diabetogenic effects, and the metabolic changes that result (42).

The placenta serves as the modulator of how and which fuels are made available to the fetus. It does so by synthesizing hormones and steroids that are lipolytic and antagonistic to insulin.

Table 6 depicts the central role of the placenta in the transfer of maternal fuels to the fetus. Glucose crosses the placenta by carrier mediated facilitated diffusion. The fetal lamb receives only one-third of the glucose that the uterus takes up from the maternal circulation (3, 60). The data indicate that, in addition to the fetus, the uterus and placenta are also important sites of glucose utilization.

In contrast, amino acids are actively tranported to the fetus (2). As a result, alanine and leucine are significantly lower in pregnant women at all periods of the 24-hour-day compared to the nonpregnant state (77).

Free fatty acids (FFA) cross the placenta in small amounts by gradient dependent diffusion and are esterified to trigylceride by fetal adipocytes. There is little evidence for selective transfer of different fatty acids, the net transfer from mother to fetus is gradient sensitive to FFA concentration on the maternal side (44).

Insulin, a large polypeptide, binds to microvillous membranes of the placenta where it is degraded but not transported to the fetus (97). The role of insulin in local placental regulation of metabolic fules has not been established. The abundance of placental insulin receptors suggests a role for the hormone in placental regulation of glucose uptake, glycogen metabolism, or lipolysis since these are physiologic effects of insulin in other tissues.

Alterations in Maternal Hormones and Metabolic Fuels during Normal Pregnancy. The overall effect of metabolic changes in pregnancy is diabetogenic and characterized by resistance to insulin. In late pregnancy, there is an augmentation of plasma insulin response to a 100-g oral glucose load without modification of resulting glucose levels (108). The daily basal insulin secretion is significantly increased relative to plasma glucose values in late gestation (19).

The mechanism(s) for the development of insulin resistance in normal pregnant women is complex and is associated with increasing maternal serum levels of HPL, progesterone, estrogens, and free cortisol (49) in addition to enhanced pancreatic secretion of insulin (53). Insulin resistance during normal pregnancy does not appear to be secondary to impaired binding of the hormone to cellular receptors on the monocyte (80); more likely the impairment in insulin action occurs as a result of a post receptor defect. The additional impact of hyperprolactinemia, hyperglucagonemia, and hypercortisolemia on insulin resistance during pregnancy requires further investigation.

Prostaglandins and Fetal Circulation. The predominant effect of prostaglandins on the fetal and maternal cardiovascular system is to maintain the ductus arteriosus, renal, mesenteric, uterine, placental, and probably the cerebral and coronary arteries in a relaxed or dilated state. The importance of the ductus arteriosus can be appreciated

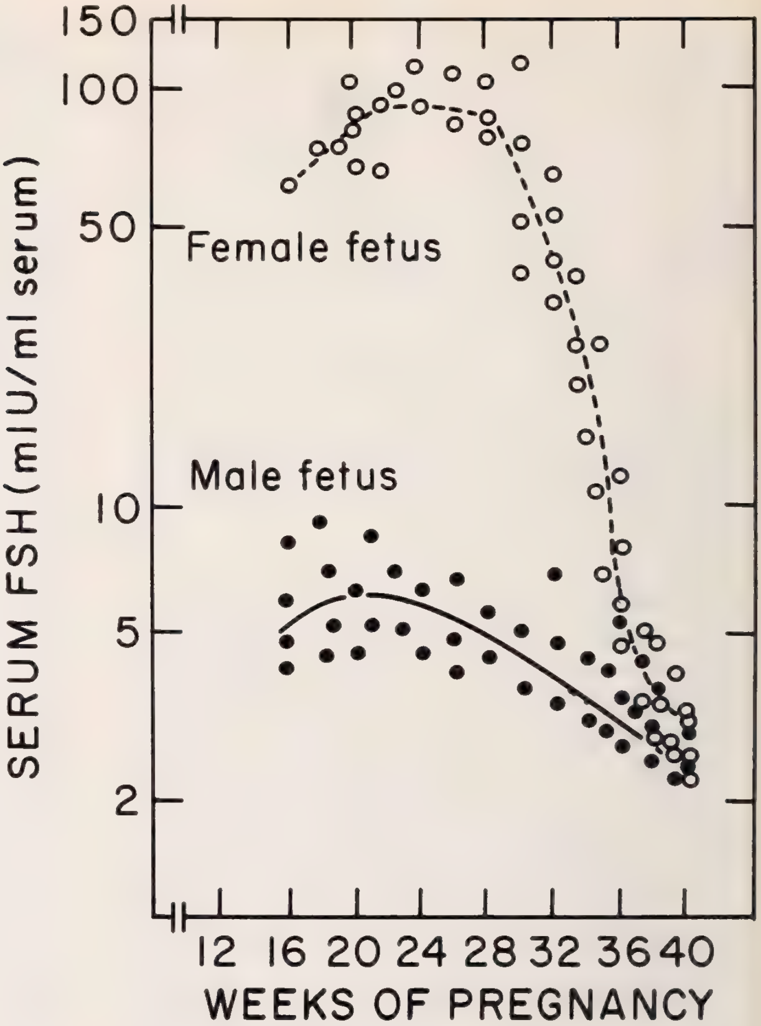

Fig. 12. Sex differences exist between fetal pituitary gonadotropin secretions in midtrimester of human pregnancy. Why female FSH is so much greater than male levels is not understood. Each eventually comes under negative feedback control by term.

by considering that 60% of the cardiac output flows through this connection between the pulmonary artery and the descending aorta.

Control of ductal patency and closure is mediated through prostaglandins. The arterial concentration of oxygen is the key to the caliber of the ductus. With increasing gestational age, the ductus becomes more responsive to increased oxygen. Attention has turned to PGI_2 and TXA_2 in this area of fetal-neonatal physiology.

Fetal lamb ductus homogenates produce mainly PGI_2 when incubated with arachidonic acid. PGE_2 and $PGF_{2\alpha}$ are formed in small amounts and TXA_2 not at all. Although PGE_2 is less abundant than PGI_2 in the ductus, it is a more potent vasodilator of the ductus and is more responsive to oxygen (decreasing vasodilation with increasing oxygen) (63). Thus, PGE_2 appears to be the most important prostaglandin in the ductus from a functional point of view, while PGI_2, the major product in the main pulmonary artery, appears to be the major factor in maintaining vasodilation in the pulmonary bed. The ductus is dilated maximally in utero, by production of prostaglandins and a positive vasoconstrictor process is required to close it. The source of the vasoconstrictor is probably the lung. With increasing maturation, the lung shifts to TXA_2 formation. This concept is consistent with the association of ductal patency and prematurity. With initiation of pulmonary ventilation at birth leading to vascular changes which deliver blood to the ductus directly from the lungs, TXA_2 now serves as the prevalent and vasoconstrictor stimulus.

Administration of vasodilating prostaglandins can maintain patency after birth, while preparing an infant for surgery to correct a congenital lesion

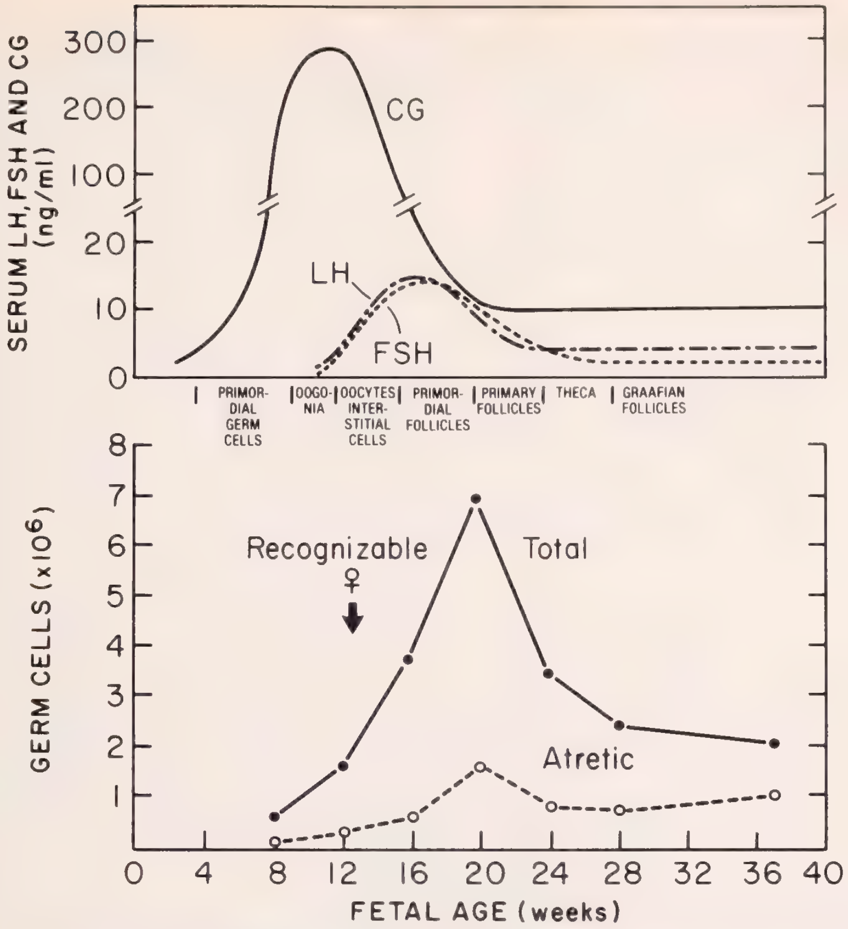

Fig. 13. What is function of female fetal pituitary gonadotropin secretion? Although this is not understood, the time relationship between gonadotropin secretion and gonadal development, differentiation, and gametogenesis suggests a cause and effect relationship.

causing pulmonary hyperfusion. On the other hand, infants with persistent ductus patency may be spared thoracotomy by treatment with an inhibitor or prostaglandin synthesis. The use of indomethacin to close a persistent ductus in the premature infant is successful about 40% of the time (17). The variable success cannot be attributed to any single factor, and further studies are necessary. At least one important factor, however, is early diagnosis and treatment. With increasing postnatal age, the ductus becomes less sensitive to prostaglandin inhibitors, probably because of more efficient clearance of the drug (7).

This aspect of the use of prostaglandin inhibitors is of concern in considering the use of agents to inhibit premature labor. The drug half-life in the fetus and newborn is prolonged because the metabolic pathways are limited, and there is reduced drug clearance because of immature renal function. In utero constriction of the ductus can cause congestive heart failure and fetal pulmonary hypertension (54, 86). Prolonged ductus constriction leads to subendocardial ischemia and fibrotic lesions in the tricuspid valve muscles. Infants with persistent pulmonary hypertension have hypoxemia, cardiomegaly, and right-to-left shunting through the foramen ovale. Infants of mothers chronically given either indomethacin or salicylates are reported to have this syndrome. Duration of exposure and dosage are critical. Occlusion of the ductus for more than 2 weeks is necessary to produce fetal pulmonary hypertension and cardiac hypertrophy. Side effects appear to be minimized when administration is limited to mothers less than 34 weeks' gestation, and when long-term use is avoided (67).

Prostaglandins, Uteroplacental Blood Flow, and Maternal Blood Pressure. A change must take place in the maternal vascular system to accommodate the volume and flow changes required

TABLE 4

Carbohydrate Metabolism in Early Pregnancy (to 20 Weeks)

Hormonal change	Effect	Metabolic change
↑ Estrogen and ↑ Progesterone	↑ Tissue glycogen storage	Anabolic
	↓ Hepatic glucose production	
↓	↑ Peripheral glucose utilization	
↑ β Cell hyperplasia and Insulin secretion	↓ Fasting plasma glucose	↑ Due to sex steroids + Hyperinsulinemia

during pregnancy. The maternal plasma volume begins to increase about the 6th week of pregnancy. It rapidly expands during the second trimester, but only slightly in the last trimester until term. There is a greater increment in plasma volume as compared to the red cell volume in normal pregnancy (mean plasma volume increase of 1074 ml vs. 350 ml increase in red cell volume) (8). In order to accommodate the increase in volume (and cardiac output) without a significant increase in the maternal blood pressure, there must be a decrease in the peripheral vascular resistance. Two mechanisms account for the decrease in resistance: one is the increasing fraction of the cardiac output which passes through the uteroplacental circulation; the other is vasodilation in the maternal vascular tree. Maintenance of both normal maternal blood pressure and uteroplacental blood flow (and therefore effective exchange functions across the placenta) depend upon controlled vasodilation, both in the systemic maternal circulation and locally within the uteroplacental unit.

Pregnancy-Induced Hypertension ("Toxemia"). There has been increasing acceptance of the concept of toxemia as a chronic problem throughout pregnancy, not an acute terminal disease manifested by a sudden expression of hypertension. Measuring the metabolic clearance rate of dehydroepiandrosterone sulfate (DS), Gant et al. (35) demonstrated a decline in DS clearance prior to the development of clinically evident toxemia. Subsequently, the same group showed that the pressor response to angiotensin II was different as early as 22 weeks in a group of primigravid women who later developed the typical clinical manifestations of toxemia at term (34). Even the routine measurement of blood pressure was able to delineate a group of women who later became hypertensive, in that they carried higher blood pressures throughout pregnancy (32).

These studies suggest that toxemia of pregnancy is caused by or is associated with a disturbance in the homeostatic mechanism responsible for maintenance of blood pressure and uteroplacental blood flow. In pregnancy, there is a need beyond the ordinary organ's concern with cellular function, i.e., the obligation of meeting the expanding demands of the growing fetus. Toxemia is associated with a 40–60% reduction in blood flow through the uteroplacental unit in women, but it has been impossible to determine whether this is a primary or secondary event. If toxemia is due to the development of impaired blood flow over a period of time, it would seem that the clinical symptoms of the disease would be a late occurrence, and subclinical abnormalities shoud be detectable earlier in pregnancy (as in the above studies). Indeed, it is generally accepted that clearance of DS reflects a decrease in uteroplacental blood flow and therefore, reduced uteroplacental blood flow preceding the appearance of hyperfusion.

Prostaglandins and Toxemia. Two properties of certain classes of prostaglandins are noteworthy in seeking the mechanism of vasodilation and regulation of blood flow in pregnancy. First, E

TABLE 5

Carbohydrate Metabolism in Late Pregnancy (20–40 Weeks)

Hormonal change	Effect	Metabolic change
↑ Human chorionic somatomammotropin	"Diabetogenic"	Facilitated anabolism during feeding
↑ Prolactin	↓ Glucose tolerance	
↑ Bound and free cortisol	Insulin resistance	Accelerated starvation during fasting
	↓ Hepatic glycogen stores	Ensure glucose and amino acids to fetus
	↑ Hepatic glucose production	

TABLE 6

Transport of Nutrients and Fuels within the Fetoplacental-Maternal Unit

Mother	Placenta	Fetus
Glucose →	Diffusion	→ Glucose
Amino acids →	Active transport	→ Amino acids
Free fatty acids →	Gradient dependent diffusion	→ Esterified to triglyceride by adipocytes
Ketones →	Diffusion	→ Ketones → Oxidation
Insulin →	Binding → | Cleavage	
Lipolytic and antagonistic to insulin ←	Synthesis Human chorionic somatomammotropin Estrogen Progesterone	

prostaglandins and prostacyclin are potent vasodilators, decreasing the peripheral resistance and systemic blood pressure by directly relaxing the smooth muscle of the arterial walls. Second, the majority of the activity of these prostaglandins appeared to be limited to the immediate vicinity of the synthesizing tissue itself (paracrine).

Initially, attention was focused on E and F prostaglandins. The important observations in the monkey (29, 95, 96), the sheep (59), the dog (101), and the rabbit (102) were as follows:

1. Angiotensin II increases uterine blood flow.
2. Angiotensin II increases PGE production by the pregnant uterus.
3. Prostaglandin synthesis inhibition lowers basal blood flow, blocks the blood flow and PGE response to angiotensin I, and raises the systemic blood pressure.

These findings were consistent with a role for E prostaglandins in maintaining the resting uteroplacental and maternal vasomotor tone, and in moderating resistance to flow in response to vasoconstrictors. In experiments in monkeys in the third trimester, angiotensin II-induced hypertension following indomethacin but failed to increase uterine artery blood flow as noted after the infusion of only angiotensin. What could account for this observation?

The entire renin-angiontensin-aldosterone system is increased in pregnancy, presumably due to a direct stimulation of substrate (angiotensinogen) synthesis by estrogen. It appears that this increase is the basic mechanism for producing the increased blood volume of pregnancy. The importance of the angiotensin-aldosterone system is underscored by fetal death noted in sheep and rabbits when angiotensin II formation was prevented by inhibiting the converting enzyme (9). The demonstration that blood vessels produce prostaglandins (1, 36, 93) led to the speculation that vascular prostaglandins were responsible for the concommitant vasodilatation associated with the increased renin-angiotensin-aldosterone activity. A pregnant woman's blood pressure at any point in time then reflects the balance of these various forces. Furthermore, a role for prostaglandins was supported by the demonstration that the administration of indomethacin or aspirin decreased the amount of angiotensin necessary to produce a pressor response in pregnant women (26). This is consistent with the conclusion the pressor responsiveness to angiotensin II during pregnancy is determined by the degree of vascular resistance to the pressor agent (33). A hypothesis was then suggested by Speroff linking estrogen, the renin-angiotensin system, and prostaglandins (Fig. 14) (93).

Estrogen may be viewed as a principal messenger for ensuring normal growth and development. Estrogen increases uterine blood flow, apparently via the mediation of a vasodilating prostaglandin (84). The major precursor for placental estrogen production is DS, secreted by the fetal adrenal gland. What regulates estrogen production has been an important question in placental physiology. This question appears to be answered with the concept that the fetal adrenal-placental unit governs its own rate of estrogen production (31). The amount of precursor available for estrogen production may be the major rate limiting factor.

Estrogen itself circulates back to the fetus to increase the production of its precursor by suppressing the activity of the enzyme, 3β-hydroxydehydrogenase, thus diverting the steroidogenic pathway to DS. This mechanism allows ever increasing levels of estrogen production. This rise in estrogens stimulates the activity of the aldosterone system to expand blood volume, and increases prostacyclin production within fetal and maternal blood flow. Toxemia of pregnancy may represent defective prostacyclin production, increased degradation of prostacyclin, a loss of response to prostacyclin, or a combination of these factors.

Prostacyclin and Toxemia. The emergence of prostacyclin as a vasodilator even more potent that E prostaglandins directed attention to this new member of the prostaglandin family. In addition, quantitation of a prostacyclin metabolite has obscured by overlap with E prostaglandins in analytic systems. Therefore, previous studies implicating E prostaglandins may actually have been dealing with prostacyclin.

Many investigators have reported a general decrease in prostacyclin associated with preeclampsia (13, 38). Lower levels of this potent vasodilator and inhibitor of platelet activity could explain three of the most significant clinical consequences of toxemia: hypertension, platelet consumption, and reduced uteroplacental blood flow.

For years, investigators have implicated disseminated intravascular coagulation (DIC) as an important component of the symptom complex associated with toxemia. Pritchard has argued that thrombocytopenia in toxemia is not an etiological factor, but a consequence of the disease, most consistent with platelet adherence at sites of vascular endothelial damage (79). A closer analysis reveals that the thrombocytopenia associated with toxemia is most similar to that seen with various microangiopathies, a consequence of abnormal platelet-endothelial interaction (4). Such a mechanism for the thrombocytopenia of toxemia is consistent with a problem in prostacyclin production or function.

As with blood pressure measurement, DS clearance, and angiotensin II pressor response, when studied in a carefully controlled manner, decreased platelet counts may also precede the development of hypertension. Early platelet consumption may be seen with preeclampsia before deterioration of urate clearance or elevation of blood pressure. The failure of heparin therapy to affect the clinical course of preeclampsia supports the thesis that DIC is not the mechanism of the

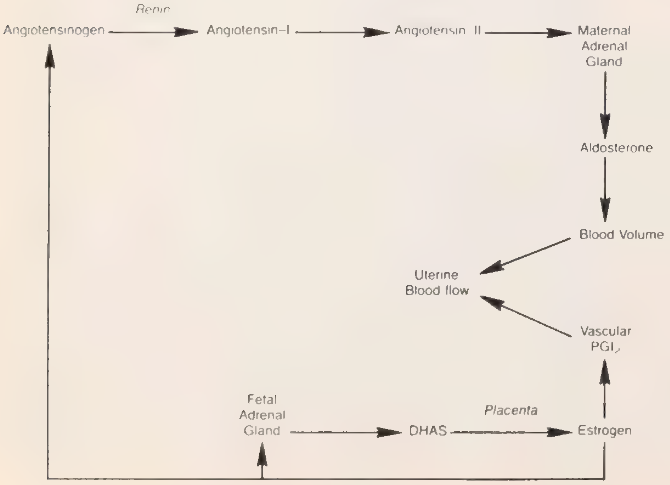

Fig. 14. Speroff's thesis suggesting that fetoplacental estrogen production governs and ensures normal growth and development is depicted in this diagram. Estrogen modifies synthesis of local prostacyclin and prostaglandins, maintains fetal adrenal gland steroid synthesis, and induces maternal hepatocyte production of renin substrate.

thrombocytopenia. That hypertension does not usually accompany the coagulation disorders associated with intrauterine fetal demise and abruptio placentae underscores this distinction; the pathophysiology of these classic problems is an infusion of thromboplastin and DIC, but not an endothelial prostacyclin disorder.

The pathologic appearance of blood vessels in the placental bed in toxemic pregnancies resembles the blood vessel changes of microangiopathic syndromes (24). Patients with the hemolytic uremic syndrome and thrombotic thrombocytopenic purpura (TTP) share a common problem: defective prostacyclin activity (45, 56). Another similar syndrome has been reported recently, a problem with a "lupus" anticoagulant (12). "Lupus anticoagulant" is a spontaneously acquired inhibitor of blood coagulation that interferes with activation of prothrombin. It is an immunoglobulin that is associated with an inhibition of prostacyclin synthesis in a variety of tissues. Although first recognized in patients with systemic lupus erythematosus, it has been detected in other clinical conditions as well. When pregnancy occurs in this syndrome, changes in the placental vessels resemble those previously believed to be exclusively associated with hypertension in pregnancy. These lesions (fibrinoid necrosis, acute atherosis, and intraluminal thrombosis) have now been described in idiopathic intrauterine growth retardation (IUGR), diabetic pregnancies, and toxemia as well as systemic lupus erythematosus. Are these examples of different diseases sharing a single mechanism: improper prostacyclin function?

Plasmaphoresis or plasma transfusion have improved the survival rate in TTP. Assuming that introduction of normal plasma restores the normal prostacyclin state in TTP, what is the effect in pregnancy hypertension? Plasma exchange has been reported in three cases of severe toxemia (23). In all three, renal function improved, and two of the three achieved healthy infants. During the exchange, less hypotensive medication was required, although eventually hypertension returned and became progressive.

Can PG synthetase inhibitors be used in an attempt to obliterate the unfavorable imbalance between prostacyclin and thromboxane? Crandon and Isherwood (20) reported a lower incidence of toxemia in patients taking aspirin compared to patients with no drug intake, and Goodlin et al (37) reported a case of severe toxemia in whom platelet counts improved with the administration of aspirin.

Although data are still limited, evidence is accumulating to link altered prostacyclin to the clinical and pathological manifestations of toxemia. Having recognized that toxemia is a chronic disease which evolves over the course of pregnancy, practical methods for early diagnosis must be sought. Therapy must begin before the irreversible end-stage disease composed of the classic triad of hypertension, proteinuria, and edema is reached.

Prostaglandins and Parturition. Perhaps the best example of the interplay among fetus, placenta, and the mother is the initiation of parturition. Endocrine changes in the uteroplacental environment are the principal governing factors accounting for the eventual development of uterine contractions. The basic work leading to this understanding has been reviewed in detail (Fig. 15) (15).

Initial work in the sheep implicated the fetal pituitary-adrenal axis in normal parturition. In this animal, the sequence of events begins about 10 days prior to labor with elevation of fetal cortisol, probably in response to fetal pituitary ACTH. Fetal adrenalectomy or hypophysectomy prolongs pregnancy, while infusion of ACTH or glucocorticoids into the sheep fetus stimulates premature labor. Maternal stimulation of the fetal adrenal is not a factor because in sheep (and in human beings) there is little or no placental transfer of maternal ACTH into the fetal circulation.

Following the increased glucocorticoid secretion by the fetal adrenal gland, the next step in the sheep is a decline in progesterone. This is brought by the induction of 17α-hydroxylase enzyme activity in the sheep placenta.

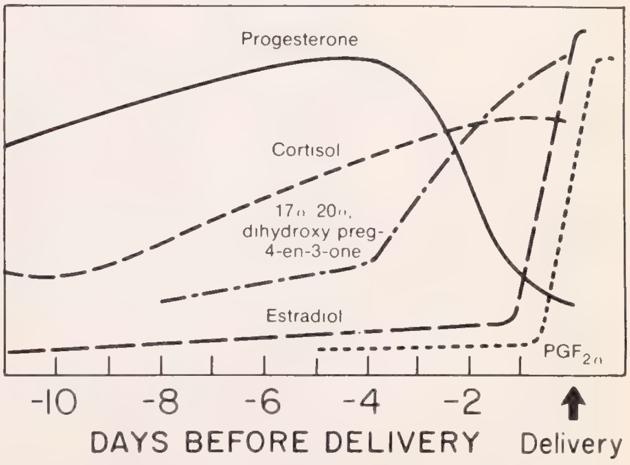

Fig. 15. Endocrine changes linked in sequential steps leading to onset of parturition in sheep.

Glucocorticoid treatment of sheep placenta tissue specifically increases the rate of production of 17α,20α-dihydroxy-pregn-4-en-3-one. This dihydroxyprogesterone compound exists in fetal sheep placental tissue obtained after spontaneous labor. Direct synthesis of progesterone does not decline, but increased metabolism to a 17-hydroxylated product results in less available progesterone. Progesterone withdrawal is associated with a decrease in the resting potential of the myometrium, i.e., an increased response to electric and oxytocic stimuli. Conduction of action potential through the muscle is increased, and myometrical excitability is increased.

Dihydroxyprogesterone is a penultimate precursor for the rise in estrogen levels which occurs a few days prior to parturition. Estrogens enhance rhythmic contractions, increases vascularity and permeability, and response to oxytocin. Thus progesterone withdrawal and estrogen increase lead to an enhancement of conduction and excitation.

The final event in sheep is a rise in $PGF_{2\alpha}$ production occurring just hours before the onset of uterine activity. A cause-and-effect relationship between the rise in estrogen and the appearance of $PGF_{2\alpha}$ has been demonstrated. The sequential decline in progesterone, the rise in estrogen, and the increase in $PGF_{2\alpha}$ are all secondary to direct induction of a placental enzyme by a glucocorticoid.

The events in human pregnancy show at least two very important differences from the ewe: a more extended time scale and a difference in progesterone "withdrawal."

While steroid changes in the sheep occur over the narrow course of several days, in human pregnancy, changes begin at approximately 34–36 weeks and progress over the last 5 weeks of pregnancy.

In human parturition, the contribution of the fetal adrenal is not cortisol but probably an effect on placental estrogen production. The common theme in human pregnancies associated with failure to begin labor on time is decreased estrogen production, e.g. anencephaly and placental sulfatase deficiency. In contrast mothers bearing fetuses who cannot form normal amounts of cortisol, such as those with congenital adrenogenital syndrome deliver on time (78).

Estrogen levels in maternal blood increase in the last trimester and are most obvious by 34–35 weeks of gestation. A later increase just prior to parturition (as in the sheep) has not been observed in human pregnancy. Although not definitely demonstrated, increased or elevated estrogen levels are thought to play a key role in increasing prostaglandin production.

As noted above, progesterone withdrawal leading to increased myometrial excitability is widely viewed as the mechanism for parturition in a variety of species. In primates, the role of progesterone is less clear, largely because of the inability to demonstrate a definite decline in peripheral blood levels of progesterone prior to parturition. A group of investigators in Dallas, Texas (99), has suggested that local regulation of biologically available progesterone may take place within the pregnant uterus by the timely appearance of a high affinity progesterone binding protein in the fetal membranes. In this thesis prior to term progesterone exists within decidual cells of the endometrium attached to and necessary for the stability of the membranes of lysosomes. With the appearance of the new binding protein in the term placenta progesterone is drawn away from the decidual. With destabilization of their membranes, lysosomes fragment and release phospholipase A_2, catalyzing prostaglandin synthesis. Decreased local levels of progesterone combined with increased levels of estrogen and prostaglandin synthesis, lead to increased myometrial activity.

Evidence for the role of prostaglandins in parturition includes the following:

1. prostaglandin levels in maternal blood and amniotic fluid increase in association with labor.
2. Arachidonic acid levels in the amniotic fluid also rise in labor. Arachidonate injected into the amniotic sac initiates parturition.
3. Patients taking high doses of aspirin show a significant increase in the average length of gestation, incidence of postmaturity, and even the duration of labor when it occurs.
4. Indomethacin prevents the normal onset of labor in monkeys and can stop premature labor in human pregnancies.
5. Stimuli known to cause the release of prostaglandins (cervical manipulation, stripping of membranes, and rupture of membranes) augment or induce uterine contractions.
6. Prostaglandins induce labor.

The availability of arachidonic acid for prostaglandin production during parturition results from hydrolysis of phosphatidylethanolamine and phosphatidylinositol in decidual, amnion, and chorion laeve tissues (73). Microsomes from amnion, chorion laeve, and decidual vera tissues contain lipases that hydrolyze fatty acids esterified in the 2 position. Specific phospholipase activity combined with a diacyglycerol lipase which also has a specificity for arachidonic acid, provides a mechanism for the release of arachidonic acid (72). The activity of these enzymes in fetal membranes and decidual vera tissue increases with increasing length of gestation.

There is little evidence that increased maternal levels of oxytocin are responsible for initiating parturition, although a low fixed level may be an essential permissive factor. Once labor has begun, however, oxytocin levels do rise, especially during the second stage. Thus oxytocin may be important for developing the more intense uterine contractions at this point in labor. Extremely high concentrations of oxytocin can be measured in the cord blood at delivery, and therefore release of oxytocin from the fetal pituitary may also play a role during labor. Indeed the magnitude of the fetal contribution to the maternal side is similar to the dose usually infused to induce labor.

Diagnosis of Fetal Jeopardy

Measurement of Estrogen in Pregnancy. Because pregnancy is characterized by an enormous progessive increase in maternal estrogen levels, and estrogen production is dependent upon fetal and placental steroidogenic cooperation, the amount of estrogen present in the maternal blood or urine reflects both fetal and placental functional well-being. Attention has been focused on estriol because 90% of maternal estriol is derived from fetal precursors. However, the end product to be assayed in the maternal blood, or urine can be influenced by processes unrelated and independent of the fetoplacenal unit. Maternal metabolism of the product as well as the efficiency of maternal renal excretion may modify the daily amount of estrogen in blood or urine. Blood flow to any of the key organs in the fetus, placenta, and mother also is important. Drugs or diseases may affect any level in the cascade of synthetic events leading to estrogen formation and may even interfere with validity of quantitative assay.

For many years measurement of estrogen in a 24-hour urine collection has been the standard method of assessing fetal well-being. This has been replaced by radioimmunoassay of unconjugated estriol in the plasma (25). Assays which measure the total plasma estriol show the same large variations from day to day as seen with the old urinary assays. Because of its short half life (5–10 min) in the maternal circulation, unconjugated estriol shows less day to day variation. Even with this more specific test available, estrogen assays of fetal condition are decreasing in utility. It is likely that in the near future other monitoring steps will have completely replaced estrogen assays (this is the case on the clinic service at Mount Sinai Hospital at this writing). Nevertheless, a short description of the methodology is included in the following paragraphs.

Normal Values and Interpretation. There are two essential clinical aspects to the use of estriol assays. First, a single specimen at any point in pregnancy is meaningless. Daily assays must be performed on morning blood samples in order to provide a serial assessment of sequential changes. For any change in concentration to be significant, there must be a decrease of approximately 40% from the mean of the previous three highest consecutive values (106). While estrogen levels in the mother are related to the size of the fetal adrenal gland and its production of precursor, there is a poor correlation between birth weight and plasma estriol levels. Macrosomia is not always associated with high estriol levels. On the other hand, excessive adrenal activity as in congenital adrenal hyperplasia can be associated with unusually high levels (14).

Problems. Drugs which affect the maternal estrogen level include corticosteroids and antibiotics. Corticosteroids administered to the mother cross the placenta poorly, and large amounts (the equivalent of 75 mg of cortisol daily) are required to suppress fetal adrenal production of estriol precursor. However, the synthetic steroids, dexamethasone and betamethasone, cross the placenta easily, and maternal estriol assessment is not reliable for at least 1 week, and sometimes 2 weeks, after the last dose (71). Antibiotics which affect the flora of the maternal gastrointestinal tract will depress maternal total estriol levels by interfering with the enterohepatic circulation. Such antibiotics inhibit the hydrolysis of the biliary estriol conjugates in the gut, preventing reabsorption and reconjugation, leading to loss of estriol in the feces (66). Total blood and urinary estriols decline, but unconjugated estriol is unaffected. Falsely elevated blood total estriols will be encountered in the presence of renal disease or when a patient is receiving oxytocin for the induction of labor because of the antidiuretic action of oxytocin. Once again, unconjugated estriol with its high metabolic clearance rate is unaffected. It is the method of choice of steroid surveillance in pregnancy.

Amniotic Fluid Estrogen Measurements. Amniotic fluid estriol is correlated with the fetal rather than the maternal estrogen pattern. Most of the estriol in the amniotic fluid is present as 16-glucosiduronate or 3-sulfate-16-glucosiduronate. A small amount exists as the 3-sulfate. Very little unconjugated estriol is present in the amniotic fluid because free estriol is rapidly transferred across the placenta and membranes. Estriol sulfate is low in concentration because the placental and fetal membranes hydrolyze the sulfated conjugates, and the free estriol product is then passed out of the fluid.

Because the membranes and the placenta have no glucuronidase activity, the glucosiduronate conjugates are removed slowly from the fetus and therefore predominate in the fetal urine and the amniotic fluid. Because of the slow changes in glucosiduronates, measurements of amniotic fluid estriol have wide variations in both normal and abnormal pregnancies. An important clinical use for amniotic fluid estrogen measurements has not emerged.

Estetrol. Estetrol (15α-hydroxyestriol) is formed from fetal precursors, and is dependent upon the 15-hydroxylation activity in the fetal liver. The capacity for 15α-hydroxylation of estrogens increases during fetal life, reaching a maximum at term. Therefore, this activity declines during infancy and is low or undetectable in adults. The use of maternal blood or urine estetrol measurements carries no advantage over the usual estriol assessment.

Clinical Uses of Estriol Assays. Assessment of maternal estriol levels has been superceded by various biophysical fetal monitoring techniques such as nonstress and stress testing, and measurement of fetal breathing and motor activity. Nevertheless in certain clinical situations (diabetes in pregnancy) the addition of estriol assays may be useful. The combination of a low estriol and a positive stress test is ominous (22). A "good" estriol level can allow expectant management of a positive stress test in the presence of an immature fetus. In other words, the estriol assay is useful in allowing the clinician to deal with false positive stress tests. Certainly patients should not be managed by estriols alone. While a low estriol and a positive stress test indicate a fetus in jeopardy, a low estriol but with a negative stress test allows postponement of intervention. It is prudent clinical practice to follow diabetic pregnancies with fetal heart rate monitoring, adding daily estriol assays when the patient is a severe diabetic, if there is a history of previous poor fetal outcome, and when a diabetic patient is hospitalized.

Estriols and Hypertension. The use of serial estriol assays in patients with toxemia has a different orientation when compared to diabetic pregnancies. While in diabetic pregnancies estriol is a means of detecting fetal distress and impending demise, in toxemia the obstetrician may use estriol measurements to be assured that the fetus is growing and doing well, and that the pregnancy may be allowed to continue until fetal maturity has been attained. Because unconjugated estriol is not excreted by the kidney, its concentration is not affected by changes in maternal renal function. A rising normal estriol level is reassuring that the fetus is doing well.

Chronically low levels of estriol during pregnancy are a grave prognostic sign for the fetus. Low estriol values during pregnancy complicated by hypertension are associated with elevated perinatal mortality (57), and in a small series, chronically low estriol excretion in toxemia of pregnancy was associated with a high incidence of neurologic defects (109).

The first-line assessment of fetal well-being in patients with hypertension is nonstress and stress testing. If a patient is hospitalized, daily estriol measurements may provide additional useful information. Chronically low estriol levels indicate fetal jeopardy, while normal rising values indicate that conservative management is justified from the fetal point of view.

Erythroblastosis Fetalis. There is no benefit to the use of estriol assays in pregnancies with erythroblastosis fetalis. Normal estriol values do not predict the condition of the fetus, and in particular, there is no correlation with the fetal hemoglobin at birth.

Prolonged Gestation. Approximately 3.5% of all pregnancies continue past the 42nd week, but not all of these postterm pregnancies result in the birth of a postmature baby. Postmature infants have a 2–3-fold increase in perinatal mortality, a higher rate of intrapartum asphyxia, a 20% incidence of neonatal hypoglycemia, and a greater tendency to develop health problems in the first 3 years of life. Interruption of the pregnancy would be a simple matter if every patient undelivered after the 42nd week of gestation could be easily delivered by induction of labor. Unfortunately, this is often not the case, and some means of diagnosing the true postmature fetus is an important clinical issue.

In prolonged pregnancies assessment of estriol levels may be rational, but usually not practical. One cannot predict which patients will carry their pregnancies to 42 weeks and beyond, therefore baseline serial assays are not available for comparison and proper judgement. The use of fetal heart rate monitoring is the most practical approach to the management of a postterm pregnancy.

Intrauterine Growth Retardation. In general, it can be stated that the failure to demonstrate a rising estriol level is consistent with a failure of the fetus to grow normally. As such, the estriol assessment is an adjunct in the biophysical evaluation of suspected growth retardation.

Placental Sulfatase Deficiency. Patients with deficient placental sulfatase are unable to hydrolize DS or 16α-hydroxy-DS, and therefore, the placenta cannot form normal amounts of estrogen. A deficiency in placental sulfatase is usually discovered when patients go beyond term and are found to have extremely low estriol levels and no evidence of fetal distress (99). All newborn children have been male, suggesting that the disorder is due to an X-linked recessive gene. The patients usually fail to go into labor and require delivery by cesarean section. The characteristic steroid findings are as follows: extremely low estriol and estetrol in the mother with extremely *high* amniotic fluid DS and *normal* dehydroepiandrosterone (DHA) and androstenedione. The normal DHA and androstenedione with a high DS rule out the adrenogenital syndrome. The small amount of estriol which is present in these patients probably arises from 16-hydroxylation and sulfatase of DS in the maternal liver, thus providing 16-hydroxylated DHA to the placenta for aromatization to estriol. Measurement of steroids derived from fetal sulfated compounds in maternal urine is a simple and reliable means of prenatal diagnosis. This can be done by measuring just one steroid, 16α-hydroxy-DHA, which can be up to 20 times increased over the normal mean value (100). Demonstration of a high level of DS in the amniotic fluid is also reliable.

Conclusion

The excitement generated by the rapid evolution in the endocrinology of pregnancy pervades our specialty. The union of fetal-maternal medicine and reproductive endocrinology and metabolism has yielded information of crucial clinical importance in many areas. How far will we have gone by the time the next review of this subject for this volume is needed? On the basis of current accomplishments, the horizon seems truly unlimited.

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Clinical Aspects of Gestational Trophoblastic Disease

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To facilitate treatment and follow-up, gestational trophoblastic disease (GTD) has been categorized into a benign component (hydratidiform mole) and a malignant component (nonmetastatic and metastatic). Hammond et al (22) have further recommended a clinical classification based on high risk factors. A modification of this classification is presented in Table 1.

Hydatidiform Mole: Partial and Complete

As stated earlier, the incidence in the United States is approximately 1/2000 hospital deliveries. Relative to the total number of births, there is an excess of HMs in the over-40 and under-20 maternal age groups (20, 33). However, the greatest number of cases occur in the 21–30 year age groups. There is a higher incidence of malignant complications in the over-40 maternal age group.

Signs and Symptoms. The patients present with a variety of manifestations (Table 2), the most frequent being vaginal bleeding, resulting from separation of molar tissue from the uterine wall. This bleeding usually begins in the late first or second trimester. The amount of bleeding may vary from spotting to hemorrhage.

The uterus is disproportionately enlarged relative to gestational age in approximately half of the cases. The remainder are either appropriate (15%) or small (35%) to gestational age (25a). Differential diagnosis based on uterine size should also include: (*a*) a normal intrauterine pregnancy with an inaccurate last menstrual period (LMP); (*b*) the presence of uterine fibroids; (*c*) an ovarian neoplasm; (*d*) multiple gestation; or (*e*) polyhydramnios.

If detected early relative to size and hCG titer, these pregnancies are easily terminated with fewer complications (Table 3). The incidence of sepsis, hemorrhage, anemia, and thyrotoxicosis increase with duration of disease and amount of viable tumor, as reflected by a high hCG titer.

When toxemia occurs prior to the 24th week of gestation, the diagnosis of molar pregnancy must be entertained. The reported incidences vary from 10–15% (4, 21). It occurs almost exclusively with markedly elevated titers and excessive uterine size.

Theca lutein cyst formation occurs in approximately 15–30% of patients with molar pregnancies. It is attributed to high levels of hCG, perhaps LH. Once the pregnancy is evacuated, these cysts will undergo spontaneous regression over a 2- to 4-month period. The indications for surgical intervention include torsion, hemorrhage, and rupture.

Differentiating the signs and symptoms of pregnancy from those associated with hyperthyroidism may be difficult. The diagnosis can be confirmed by thyroid function testing, including free serum thyroxine and T_3. Purified hCG has been found to have intrinsic thyroid stimulating activity (29, 34). Thus, those patients with markedly elevated titers of hCG for a protracted period of time are more likely to manifest symptoms of thyroid dysfunction. Only 8–10% of these patients will develop thyrotoxicosis (4). The life-threatening complications of thyroid storm may be precipitated by toxemia, infection, surgery, or anesthesia. Symptoms include delirium, convulsions, coma, hyperthermia, atrial fibrillation, or cardiovascular collapse. Prompt and aggressive treatment with β-blockers, iodide, and antithyroid medication is required.

A serious complication reported in 27% of patients with uteri larger than 16 weeks is acute pulmonary insufficiency (41). This complication

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TABLE 1

Gestational Trophoblastic Disease

I. Benign gestational trophoblastic disease
    A. Hydatidiform mole
        1. Complete
        2. Partial
II. Nonmetastatic malignant gestational trophoblastic disease
    A. No evidence of disease outside uterus
        1. Persistent trophoblastic disease, i.e. invasive mole (chorioadenoma destruens) choriocarcinoma localized to uterus
III. Metastatic malignant gestational trophoblastic disease
    A. Good prognosis
        1. Duration of disease from termination of pregnancy prior to initiation of chemotherapy is less than 4 months
        2. Pretreatment urinary hCG titers is <100,000 IU/24 hr or serum β-hCG is <40–50,000 mIU/ml
        3. Metastatic disease limited to pelvis or lungs
        4. No significant prior chemotherapy
    B. Poor prognosis
        1. Duration of disease from termination of pregnancy prior to initiation of chemotherapy is more than 4 months
        2. High pretreatment titer >50,000 mIU/ml. (serum β-hCG)
        3. Brain, liver, GI metastatic lesions
        4. Significant prior chemotherapy
        5. Metastatic choriocarcinoma following term gestation

is manifested usually within 4 hr of evacuation by cough, chest pain, tachypnea tachycardia, and cyanosis. On auscultation of the chest, rales may be heard. The chest x-ray may show diffuse infiltrates. The syndrome has been ascribed to massive deportation of trophoblastic tissue occluding small vessels leading to pulmonary hypertension and right heart failure. Pulmonary edema secondary to hypervolemia, hyperthyroidism, or cardiac dysfunction has also been implicated in the etiopathogenesis. Insertion of a Swan-Ganz catheter to aid in management of the cardiovascular instability may prove helpful.

Laboratory Tests. Once suspected, the diagnosis can be confirmed by ultrasound (sonography), hCG titer, aminography if ultrasound is not readily available and, rarely, pelvic arteriography.

TABLE 3

Complications Associated with Hydatidiform Mole

1. Anemia
2. Sepsis
3. Hemorrhage
4. Acute pulmonary insufficiency
5. Trophoblastic embolization
6. Thyroid storm

TABLE 2

Presenting Signs and Symptoms in Hydatidiform Mole

1. Vaginal bleeding → early abortion, passage of vesicular tissue
2. Nausea and vomiting → hyperemesis
3. Uterine enlargement disproportionate to gestational age
4. Toxemia
5. Adnexal masses (theca lutein cyst)
6. Hyperthyroidism → thyrotoxicosis → high output cardiac failure

Amniography is rarely, if ever, used at our institution. It is an invasive technique. It may be technically difficult, as there is usually no amniotic fluid. If amniotic fluid is not obtained, the diagnosis should be suspected. The uterus must be at least 14–16 weeks in size before attempting the procedure. The procedure involves the percutaneous transabdominal intrauterine instillation of radiopaque dye, usually 10 ml of 50% diatrizoate (Hypaque) and 10 ml of normal saline. A characteristic honeycomb or moth-eaten pattern is seen. The complications, although minor, include: infection, abortion, premature labor of a normal pregnancy inadvertently, x-ray exposure although minimal, and extravasated injection.

Sonography is the method of choice as it is noninvasive and capable of assessing the ovaries and pelvis as well. It is indicated with any bleeding observed in the first half of pregnancy. It can be used to assess the involution of enlarged ovaries and can exclude an intrauterine pregnancy in the post-molar evacuation follow-up of patients (Fig. 1).

The sonographic picture is influenced by the type of scanner used, the type of mole (i.e. complete, partial, invasive), and the timing of the sonogram (i.e. trimester). The β-scan apparatus gives the classical "snowstorm" picture (Fig. 1). The gray scale imaging allows better visualization of the vesicular structure of the molar tissue. The real time scanners are capable of capturing the characteristic quivering of the fluid-filled vesicles (15). In the first trimester at less than 8 weeks, the sonographic picture may reveal an abnormal gestational sac. If repeated in 2 or 3 weeks, a more characteristic picture may have developed. Molar tissue visualization depends on the amount of tissue present in the uterus and the extent of secondary change, such as hemorrhage.

Pelvic arteriography is less useful as an initial diagnostic tool. It is technically difficult and exposes the patient to radiation. Early bilateral filling of the uterine veins, presumably on the

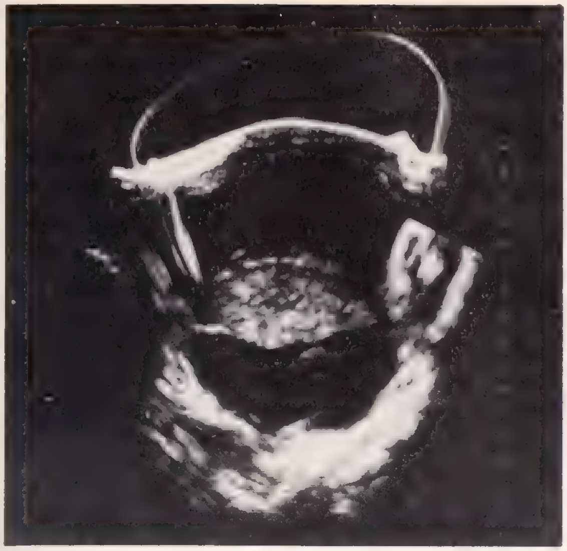

Fig. 1. Sonographic picture of uterus with "snowstorm" pattern (center of picture) and bilateral theca lutein cysts (clear spaces at lower portion).

basis of A-V shunting, is seen. This test is more useful in detecting a residual focus of viable tumor in nonmetastatic trophoblastic disease.

Numerous biochemical serum and urine measurements have been reported to aid in the differential diagnosis of normal pregnancy and HM. These include human placental lactogen (hPL), total estrogens, estradiol, estriol, estetrol, pregnanediol, progesterone, alkaline phosphatase leucine aminopeptidase oxytocinase, α-fetoprotein (αFP), carcinoembryonic antigen (CEA), pregnancy specific-β-1-glycoprotein (SPI), placental protein 5 (PP5), and human chorionic gonadotropin (hCG) and its α- and β-subunits. Clinically, the most useful test to date is the hCG and its β-subunit. hCG is an obligate secretory product of the syncytiotrophoblast. The α-subunit is nearly identical to the α-subunit of LH, FSH, and TSH. The β-subunit gives these hormones their biologic and immunologic specificity. β-hCG differs from the β-subunit of LH by the addition of a 30-amino acid carboxyl-terminal sequence (10). Normal pregnancy hCG peaks between weeks 9 and 14 (approximately day 60–100). A continued rise in hCG beyond the 14th week is suggestive of a molar pregnancy. The diagnosis cannot be based on a single value. The differential diagnosis should include: (*a*) a normal intrauterine pregnancy with inaccurate LMP (normal pregnancy is usually associated with less than 100,000 IU/24-hr urine); and (*b*) multiple gestation may be associated with values of 500,000 IU/24-hr urine (33).

This elevated hCG promotes ovarian steroidogenesis, thus resulting in elevated estrogen and progesterone. In addition, the trophoblastic tissue is capable of producing estrogen and progesterone.

Initial Treatment and Follow-up. Having confirmed the diagnosis, the pregnancy must be terminated. In the past, mortality was as high as 10% secondary to hemorrhage, infection and uterine perforation. It is now less than 1% (11). The mode of evacuation is determined by the patient's condition, amount of bleeding, age and parity, uterine size, and desire for future reproduction. Suction curettage is often the method of choice together with intravenous oxytocin (Fig. 2). Uteri as large as 24 weeks have been successfully evacuated by this method. Some advocate sharp curettage at the end of the procedure, with these curettings submitted separately. Hysterectomy may be the treatment of choice with markedly enlarged uteri, with vigorous and excessive uterine bleeding and in the elderly multiparous patient. As age is an important determinant, the older, more parous woman is at an increased risk of malignant sequelae (Table 4). Primary hysterectomy can decrease this risk by preventing malignant change in the uterus but not that developing in deported trophoblastic cells.

Postevacuation spontaneous remission in HMs can be expected in 80–85%; the remaining 15–20% will have persistent disease. Approximately 5% progress to choriocarcinoma. In the United

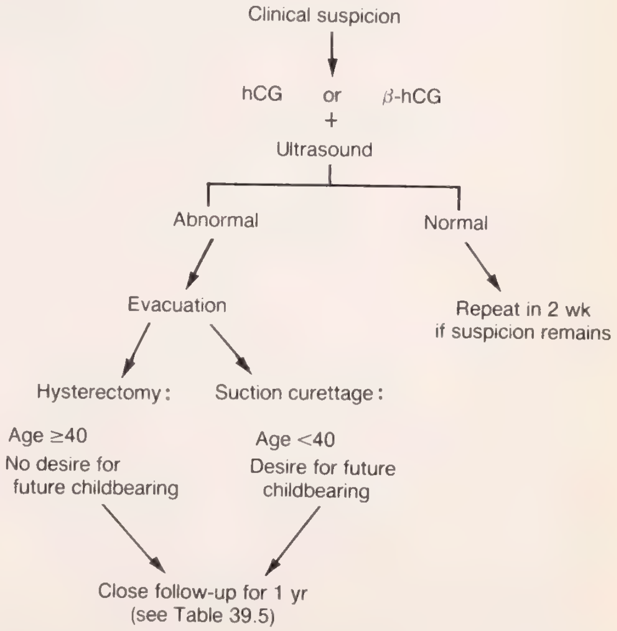

Fig. 2. Diagnosis and initial management of hydatidiform mole.

TABLE 4

Hydatidiform Mole: Risk Factors Predicting Progression to Malignant Sequelae

1. Maternal age ≥40 years
2. Level of hCG titer >100,000 mIU/ml
3. Rapid tumor growth as reflected in uterine size (i.e. large for dates)
4. Enlarged ovarian (theca lutein) cysts (5–6 cm)
5. Others
   a. Complete mole by histologic examination
   b. ABO blood groups: group A women married to group O men and group O women married to group A men
   c. Excessive postevacuation uterine bleeding
   d. Acute pulmonary insufficiency
   e. Toxemia
   f. Disseminated intravascular coagulation

States, approximately half of the patients with metastatic trophoblastic disease and 75% of the patients with nonmetastatic trophoblastic disease develop these tumors as sequelae to molar pregnancy (11, 26, 36). Several risk factors have been identified to better predict which cases will result in persistent disease (Table 4). A combination of these factors increases the risk considerably. Trophoblastic cells express Rh^0 blood group antigens on their surface membranes. Thus, it is advised to give Rh^0(D) immune globulin to all previously nonsensitized Rh-negative women following molar evacuation (7).

Regardless of the method of evacuation, close follow-up of *all* patients is the key to successful management (Table 5). A chest x-ray should be obtained initially at the time of diagnosis or evacuation. This should be repeated if the serial hCG titers plateau or rise. Pelvic examination should be performed every 2–4 weeks until the hCG titers return to normal. Once normal levels have been achieved, repeat pelvic examinations should be performed every 3 months for 1 year. If theca lutein cysts have been detected by examination or sonography, their regression over a 2- to 4-month period can be documented by serial sonograms.

HCG titers should be obtained at 1-week intervals until they are normal, plateau, or elevate. Immunologic pregnancy tests are useful only when positive, usually at sensitivities greater than 1000 IU/24 hr. Quantitative immunoassays may be used until the titer drops below their sensitivity, then a more sensitive assay is required. The β-subunit provides such an assay (41a). At present, the β-hCG is detected in serum. It has been suggested that radioimmunoassay of urinary β-hCG may be far more sensitive (44). Radioimmunoassays for the β-chain of hCG allow sensitive detection of hCG without significant cross-reaction with pituitary LH. The lower level of sensitivity of such a β-subunit radioimmunoassay for hCG in our lab is 7.5 mIU/ml Table 6). At this level of sensitivity, no fewer than 10^4–10^5 cells can be detected. The hCG titer correlates with the amount of viable trophoblastic tissue. The hCG titers should be plotted on a logarithmic regression curve. An hCG regression curve is a function of: (*a*) preevacuation hCG titer, (*b*) postevacuation production of hCG by a progressively decreasing volume of viable trophoblastic, and (*c*) excretion of hCG. A regression curve can facilitate the early recognition of persistent disease (33, 38). Remission is defined as three consecutive negative β-hCG titers.

Pregnancy should be avoided during the postmole follow-up. Effective contraception should be practiced for at least 1 year. The intrauterine device (IUD) is not an acceptable method because of the bleeding irregularities associated with its use. The oral contraceptive (OCP) is ideal as it is 99% effective and suppresses the midcycle LH surge. However, Stone et al. (39) reported persistent hCG titers in users of OCP. Twenty-five percent of users of OCP required chemotherapy as compared to ten percent using other methods. They proposed exogenous steroid induction or enhancement of trophoblastic neoplasia. Berkowitz et al (8) in a well controlled study were not able to duplicate this finding. The controls were equally matched for all of the risk factors, including age, preevacuation titers, and uterine size. In vitro studies also failed to confirm this enhancing effect (16). In view of these more recent studies, OCP can be used unless contraindicated for a medical reason (i.e., hypertension, age greater than 35 yr, particularly in a smoker, etc.).

As most of these patients are young, they are quite concerned about future reproduction. Repeat molar pregnancy occurs in from 1.2–3% of subsequent pregnancies (27). Subsequent preg-

TABLE 5

Follow-Up of Hydatidiform Mole

1. Follow hCG at weekly intervals:
   a. When titers <100 mIU/ml, may follow every 2 weeks
   b. Follow every 2 weeks until three consecutive hCG titers are negative in the β-subunit assay
   c. Titers every month for 6 months
   d. Titers every 2 months for 6 months
2. Pelvic examinations every 2–4 weeks until hCG is negative; then every 3 months for 1 year, supplement with ultrasound as needed
3. Initial chest x-ray; repeat if hCG plateaus or rises.

TABLE 6
Commonly Used Pregnancy Tests

Assay	Approximate Sensitivity (*IU hCG/liter*)	Test Time
A. Urine hCG assay		
1. Immunologic		
a. Latex agglutination, slide	700–1000	2 min
b. Latex agglutination inhibition, slide	2000–5000	2 min
c. Hemagglutination inhibition, tube	500–2000	2 hr
B. Blood hCG assay		
1. Immunologic		
a. Hemagglutination inhibition, tube	500–1000	2 hr
b. Radioimmunoassays, β-subunit	7.5 mIU	6–24 hr
2. Biologic		
a. Radioreceptor (RRA) bovine corpus luteum	6–200	1–3 hr

nancies should have a sonogram done in the first trimester. The placenta or curettings should be submitted to the pathologist for examination in all subsequent pregnancies. The β-hCG titer should be obtained at 6 weeks following all subsequent pregnancies. In the 912 patients followed at the New England Trophoblastic Disease Center, there was no increased risk of stillbirth, congenital anomalies, prematurity, ectopic pregnancy, obstetric complications, or infertility. There was a slightly increased incidence of spontaneous abortion (18%). This was attributed to meticulous clinical scrutiny and hCG monitoring (35).

Chemotherapy. Usually chemotherapy is instituted because of an abnormal regression curve. If spontaneous titer remission occurs but the regression curve is not normal, hCG titers should be followed monthly for 1 yr. A steadily falling hCG portends a favorable outcome. Initially, some investigators suggested that chemotherapy be started if the hCG titers were not within normal range by 60 days. Subsequent data indicates a dropping titer, although not negative at 60 days, may be followed as long as there is no plateau or rising hCG titer (13). The most critical period of follow-up is the first 4–6 weeks (33). In patients with elevated hCG titers at 8 weeks (approximately 60 days) postevacuation, there is a 50% incidence of subsequent development of either invasive mole or choriocarcinoma (21).

The role of prophylactic chemotherapy is controversial. The rationale for its use is to reduce the development of either invasive mole or choriocarcinoma. When initially proposed, all patients were treated with a single agent for a 5-day course. However, due to the toxicity of chemotherapy and the future reproductive capacity of these young women, most investigators believed this was too radical a treatment. It should be rememberedthat 80–85% undergo spontaneous remission postevacuation. Proponents of prophylactic treatment (20) have now modified their approach. Patients with *low risk molar* gestation undergo either suction evacuation or hysterectomy without prophylaxis. Patients with *high risk molar* gestation (Table 4) get prophylactic actinomycin D (Act D) 12 μg/kg/day for five daily doses. Treatment is started 3 days before evacuation. Serial hCG titers are obtained postevacuation as described in Table 5. Some investigators believe that even this approach is too radical. By closely following the patients as outlined, 100% of patients with malignant sequelae of hydatidiform mole are cured by present day technique (21). Prophylactic chemotherapy may be suitable for patients who are poorly compliant and may get lost to follow-up. It should be noted, however, that none of the prophylactic regimens prevents the development of malignancy in *all* of the patients treated.

Systemic chemotherapy is indicated if: (*a*) the hCG titers fails to fall to normal pituitary range or negative in the β-subunit assay; (*b*) the hCG titer plateaus for 2–3 weeks or rises significantly for 2 weeks; (*c*) metastases are detected; (*d*) a tissue diagnosis of invasive mole or choriocarcinoma is made; or (*e*) there is postremission hCG titer elevation.

The patient with elevated or plateaued hCG titers will require further treatment. The role of repeat D&C postevacuation with elevated titers is controversial. If the patient is bleeding, the D&C may stop the hemorrhage. Advocates of this procedure further reason that there may be residual disease which will be removed by repeat curettage. In the patient who is not bleeding or in patients with normal curettings on the repeat D&C, treatment is indicated on the basis of elevated hCG titers. The D&C may not be helpful as the disease lies deeply in the myometrium or the patient may have metastatic disease responsible for the titer elevation. These patients must be thoroughly examined and staged. This group of persistent trophoblastic disease can then be classified as nonmetastatic trophoblastic disease or metastatic gestational trophoblastic disease or metastatic gestational trophoblastic disease, good or poor prognosis (Table 1). Once this is done, appropriate treatment can then be instituted.

Malignant Trophoblastic Disease: Nonmetastatic and Metastatic

The incidence of invasive mole is given as 1/12,000 pregnancies (21). Persistent trophoblastic tissue remains localized to the uterus in approximately 10–15% of patients following evacuation of molar pregnancy. In untreated patients, there is a high incidence of spontaneous uterine perforation, intraperitoneal hemorrhage or severe vaginal hemorrhage. The incidence of choriocarcinoma is given as 1/40,000 pregnancies (21). Hydatidiform mole precedes approximately 50% of the cases. The remaining half are equally distributed between normal pregnancy (25%), abortion or ectopic pregnancy (25%). This classification is less useful today (21).

Signs and Symptoms. The cardinal sign of malignant trophoblastic disease is vaginal bleeding (Table 7). The majority of patients presenting with active bleeding will have uterine pathology. It should be kept in mind, however, that the vagina is a frequent site of metastasis and may be responsible for the bleeding. In patients with nonmetastatic disease, the residual disease may lie deeply in the myometrium, beyond the reach of a curette. An additional point to remember is that 20–30% of patients with metastatic disease may have no disease remaining in the uterus (23). Thus, it is readily apparent that a D&C may not be helpful in some of these cases. Malignant trophoblastic disease may present as a surgical emergency. An acute abdomen may result from a spontaneous uterine perforation, a ruptured or leaking theca lutein cyst, a bleeding ovarian metastasis, or a ruptured liver.

TABLE 7

Signs and Symptoms in Malignant Trophoblastic Disease (Metastatic and Nonmetastatic)

1. Vaginal bleeding
2. Abdominal pain
    - Right upper quadrant pain
    - Pelvic pain
    - Acute abdomen
3. Respiratory symptoms
    - Cough
    - Hemoptysis
    - Pleuritic chest pain
4. Neurologic symptoms
    - Headache
    - Localized neurologic deficits
    - Stroke
    - Coma
    - Tumor
5. Unexplained GI or GU bleeding

Malignant trophoblastic disease is the great masquerader. The presenting complaint in metastatic disease depends on the organ involved. Female patients in the reproductive age group presenting with unexplained pulmonary symptoms, neurologic symptoms, GI or GU bleeding should have a β-hCG drawn. This assay is preferred for its sensitivity. Approximately 25% of patients with nonmetastatic malignant trophoblastic disease have gonadotropin titers in excess of pituitary levels but below that required for a positive pregnancy test with the usual assays (<1000 IU/24 hours) (26). The normal pituitary produces up to 4 IU/24 hr if the gonad is nonfunctional (castrate or menopausal) (21).

Approximately half of the patients with metastatic trophoblastic disease and 75% of patients with non-metastatic trophoblastic disease develop these tumors as sequelae to molar pregnancies (11, 26, 36). The remainder follow abortion, ectopic or term pregnancies. The duration of time from pregnancy to diagnosis is highly variable but is a very important prognostic factor (Table 4). The longest interval recorded is 17 years (2). Patients with irregular bleeding post-termination of any pregnancy should have a quantitative β-hCG drawn. The mean hCG-β-positive intervals posttermination of first and second trimester pregnancies and term pregnancies are given in Table 8 (27).

Laboratory Testing. After confirmation of the diagnosis of malignant trophoblastic disease with a β-hCG titer, the patient should have a thorough history and physical examination as well as a battery of tests (Table 9) to detect any metastatic lesions (Table 10). The purpose of this testing is to accurately identify metastatic disease so that the patients can be placed in the proper risk category and receive the appropriate chemotherapy. A variety of lesions can be seen on chest x-ray. The most common is the discrete "cannonball" metastasis. Isotopic liver and brain scans may not detect very small foci of the disease. These tests can be supplemented with ultrasonography and computed axial tomography (CAT) scans. The CAT scan can detect density differences as small as 0.5%.

To identify those patients with brain metastasis, Bagshawe and Harland recommend (3) determining the hCG plasma/cerebral spinal fluid ratio. A ratio of less than 60:1 is considered diagnostic of cerebral metastasis. Other investigators (9) believe that this ratio does not conclusively prove or exclude central nervous system (CNS)

TABLE 8
Mean hCG-β-Positive Intervals in Normal Pregnancy

Interval	Intact uterus	Hysterectomy	Hysterectomy & hypogastric ligation
1. First trimester Induced abortion	37 days range: 27–44 days	16 days (only 1 patient)	
2. Second trimester Induced abortion	27 days range: 16–40 days	39 days 29–45 days	12 days (1 patient)
3. Normal term delivery	range: 11–16 day (only 2 patients)		

metastasis. Others (37) believe the ratio should be less than 30:1. At the present time, the decision to treat CNS disease should not be based on a single lumbar puncture value. The findings from a lumbar puncture should be corroborated with other diagnostic data and the clinical presentation. Prior to lumbar puncture, the fundi should be examined for papilledema and venous pulsation to avoid herniation of the brain.

Radioimmunolocalization of tumors has been described in localizing viable tumor (6, 24). Radiolabeled antibody directed against human chorionic gonadotropin is injected into the patient. Tumors as small as 1–2 cm in diameter and producing hCG in the region of 500–1000 mIU/ml can be localized. This procedure, currently done only at highly specialized centers, is reserved for patients with tumors resistant to the standard treatment regimens.

Management

Nonmetastatic Trophoblastic Disease. Patients with nonmetastatic trophoblastic disease desiring future reproduction are treated with single agent chemotherapy. If the patients are greater than 40 yr of age and have completed childbearing, a total abdominal hysterectomy is performed on the 3rd day of the first 5-day course of single drug chemotherapy. There is no increase in postsurgical morbidity in patients receiving these agents concomitant with surgery (23, 31). Chemotherapy is continued postsurgery if the titers are elevated. Some advocate one to three additional courses once a negative β-hCG is obtained. The amount and duration of chemotherapy is less when combined with total abdominal hysterectomy (23). The ovaries may be preserved.

Methotrexate (MTX) is classified as an antimetabolite. The dosage is 0.4 mgm/kg day I.M. or I.V. for five daily doses. It is contraindicated in patients with impaired hepatic or renal function. An alternative choice equally effective is Act D. This drug intercalates between DNA base pairs and inhibits DNA-dependent RNA synthesis. The dosage is 10–13 μg/kg I.V. daily for 5 days. It the drug is extravasated during administration, tissue necrosis will occur. Repetitive 5-day courses should be planned with a minimum interval between courses of 7 days but a maximum interval not to exceed 14 days unless laboratory values or toxicities dictate otherwise. If the hCG titer fails to decline, plateaus, or if there is a 10-fold rise through two courses of chemotherapy, the alternative drug is given. If there is evidence of metastasis, the drugs should be changed. MTX with citrovorum factor (CF) has been used with

TABLE 9
Work-Up of Patient with Malignant Trophoblastic Disease

1. Thorough physical examination, including detailed neurologic examination
2. Stool guaiac: if positive, barium enema or upper GI series, as indicated
3. CBC with platelet count and differential
4. Liver and renal function chemistries
5. Chest x-ray, possibly tomograms
6. Isotopic liver and brain scans
7. Pelvic and abdominal sonogram
8. CAT scan: brain, whole abdomen and pelvis
9. EEG
10. IVP if indicated
11. Lumbar puncture (see text)
12. Cerebral angiography, if indicated

TABLE 10
Metastatic Trophoblastic Disease: Sites of Metastases

1. Lung
2. Lower genital tract (cervix, vagina, vulva)
3. Brain
4. Liver
5. Kidney
6. GI tract
7. Ovary
8. Rarely: gingiva, skeletal muscle, mediastinum

equally good results. MTX is given at a dose of 1 mg/kg every other day for four doses. CF is administered intramuscularly at a dose of 0.1 mg/kg given 24 hr following each dose of MTX. Goldstein et al. (19) recommend repeating this treatment when and if the hCG level plateaus for more than 2 consecutive weeks, become elevated, or if metastases appear. Hammond et al (23) prefer to repeat this treatment at 7-day intervals and to continue with one additional course after reaching a negative β-hCG.

Hematologic parameters must be carefully monitored. Prior to repeating a course of chemotherapy, white blood cell counts must be greater than 3000/mm^3 with polymorphonuclear cells greater than 1500/mm^3 and platelet counts must be greater than 100,000/mm^3. Liver and renal function chemistries must be within normal limits.

The toxicities (Table 11) are numerous and require careful observation and supportive measures. At the nadir of the patients' blood counts, platelet transfusions, leukocyte transfusions, intravenous hydration, and antibiotics may be required.

Chemotherapy is continued for one to three additional courses after reaching a negative β-hCG. The rationale for this is based on the current limitations of the sensitivity of the β-hCG. No fewer than 10^4–10^5 cells can be detected. Remission is defined as three negative consecutive β-hCG titers. After treatment is completed, the patients require careful follow-up for a year (Table 12).

For those patients not responding to the above treatment protocol, surgery may be necessary. The role of surgery as a primary modality has been previously discussed. In patients with plateaued or rising hCG titers and disease limited to the uterus, a total abdominal hysterectomy (TAH) is indicated. Prior to a TAH, a metastatic work-up must be done to rule out disease elsewhere. Pelvic sonography, CAT scan or pelvic arteriography may demonstrate a focus of trophoblastic disease in the myometrium. In patients highly motivated to retain their reproductive capacity, bilateral hypogastric arterial infusion using MTX or Act D has been successfully reported (23, 32). Surgery may also be required for the control of hemorrhage, adnexal accidents, relief of urinary obstruction, or drainage of abscesses (31).

TABLE 11

Toxicities from Methotrexate (MTX) and Actinomycin D (Act D)

1. Gastrointestinal:
    - Stomatitis, diarrhea
    - Anorexia, nausea and vomiting (Act D)
    - Hepatic dysfunction (MTX)
2. Hematologic:
    - Leukopenia, anemia, thrombocytopenia
3. Dermatologic:
    - Alopecia—usually reversible
    - Dermatitis
    - Local irritant (Act D)
4. Renal (MTX)

Late recurrences are unusual. Hammond et al. (23) report a 2.1% recurrence in this group following the diagnosis of remission. They recurred within the 1st yr and were all successfully treated. When the above treatment protocol is followed, the prognosis is extremely good. A 100% cure rate can be obtained, with 90% retaining their reproductive potential (23).

The fertility and subsequent pregnancies do not seem to be adversely affected. There may be a slightly increased risk of placenta accreta (42) and spontaneous abortion, which may be related to close follow-up. A sonogram should be done in the first trimester of all subsequent pregnancies. The placenta and curettings from abortions should be submitted for pathologic examination. A β-hCG should be sent at 6 weeks post termination of all subsequent pregnancies.

Metastatic GTD. In patients with metastatic GTD, it is important to correctly divide those with good and poor prognosis (Table 1). The opportunity for cure in patients with poor prognosis GTD is maximized by early detection and aggressive multimodality therapy. These patients should be treated with combination chemotherapy as the initial treatment (22).

Good Prognosis. Patients with good prognosis metastatic GTD are treated with MTX or Act D as outlined for nonmetastatic GTD (Fig. 3). Weekly hCG titers are followed. If the titer fails to decline through two courses of chemotherapy or a normal hCG titer is not achieved after four or five courses of one drug, the alternative drug is instituted. The chemotherapy is continued for one to three courses after achieving a negative hCG titer. Remission is defined as three consec-

TABLE 12

Follow-Up in Nonmetastatic and Metastatic GTD

1. β-hCG titer every 2 weeks for 3 months, then every month for 9 months, then every 2 months for 12 months, then every 6 months indefinitely
2. Chest x-ray and pelvic examinations every 3 months for 1 year then every 6 months for one year
3. Contraception for 1 year

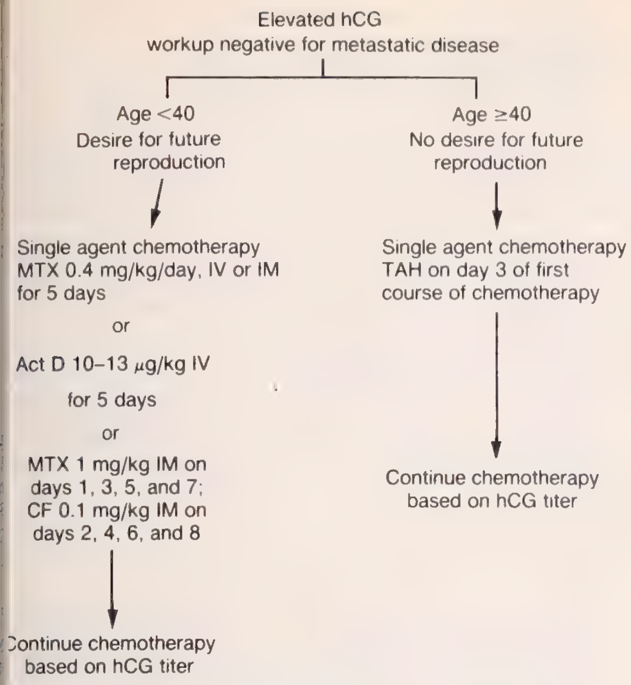
Elevated hCG
workup negative for metastatic disease
Age <40
Desire for future reproduction
Age ≥40
No desire for future reproduction
Single agent chemotherapy
MTX 0.4 mg/kg/day, IV or IM for 5 days
or
Act D 10–13 μg/kg IV for 5 days
or
MTX 1 mg/kg IM on days 1, 3, 5, and 7; CF 0.1 mg/kg IM on days 2, 4, 6, and 8
ontinue chemotherapy based on hCG titer
Single agent chemotherapy
TAH on day 3 of first course of chemotherapy
Continue chemotherapy based on hCG titer

Fig. 3. Management of nonmetastatic GTD and good prognosis metastatic GTD.

utive negative hCG titers. More courses of chemotherapy will be required as compared to nonmetastatic GTD. If the hCG titers reflect resistance to MTX and Act D, the patient should be switched to multiagent regimen (see below). Surgery may be required if there is evidence of localized persistent disease, e.g. a lung nodule or nodule in the myometrium (23, 40). Pelvic arterial infusion may also be attempted in those women strongly motivated to maintain their reproductive potential (32). Surgery may also be required for hemorrhage, adnexal accidents, urinary tract obstruction, or abscess drainage (31). In the Hammond et al series (23), there was a 5.4% recurrence rate, all of whom were successfully treated with chemotherapy. With this multimodality approach and close follow up, a 100% remission rate is obtainable. In the same series (23) almost 90% were able to maintain their reproductive function. As previously noted, in subsequent pregnancies, there may be a slightly increased incidence of spontaneous abortions and placenta accreta.

Poor Prognosis. Patients with poor prognosis metastatic GTD require multiagent chemotherapy as initial chemotherapy. The response rate is not as good if they have failed single agent chemotherapy. The decline in remission rate is related to more extensive and resistant disease as well as to myelosuppression from an exhausted bone marrow. Radiotherapy (RT) and surgery play supplemental roles. RT is recommended with extrinsic liver metastasis and brain metastasis. It seems to lessen the likelihood of acute hemorrhage and may play a synergistic role when combined with chemotherapy. Surgery is indicated to control bleeding, infection, or intestinal obstruction. Hysterectomy is indicated for hemorrhage or perforation or as a primary treatment in women over 40 yr of age or those who have completed their childbearing. Twenty to thirty percent of patients (23) have no disease remaining in the uterus. Pelvic sonography, CAT scanning or pelvic arteriography can aid in determining the presence or absence of disease. A TAH or curettage may enhance the prognosis and reduce the duration and amount of chemotherapy required for cure (21).

The chemotherapy recommended is given in Table 13. This MTX-Act D-chloroambucil (MAC) regimen is given daily for 5 days, and ideally repeated every 12–14 days. The interval should be greater than 10 days but less than 21 days. The treatment regimen may have to be modified according to toxicities. Therapy is continued until the β-hCG is negative. Remission is defined as three consecutive negative β-hCG titers. Townsend and Morrow (33) recommend continuing treatment for 6 months after remission with either MTX or Act D because of the high relapse rate. Hammond et al (23) recommend two to five courses of systemic chemotherapy after remission status has been achieved. If the hCG titer during treatment plateaus or rises after two courses of MAC, alternative therapy is instituted with either the Bagshawe (1), modified Bagshawe regimen (22, 43), or Einhorn and Donahue regimen (14).

With this intensive chemotherapy regimen, severe toxicity can result. The physician must be prepared to transfuse platelets, leukocytes, blood, and blood products. Hyperalimentation may be required to maintain the adequate nutritional status of the patient.

In patients treated *initially* with combination chemotherapy, usually in combination with surgery and/or radiotherapy, 70–80% cure rates can be achieved (30). Some patients are left with residua of disease or treatment such as neurological

TABLE 13
Chemotherapy for "Poor" Prognosis Metastatic GTD

1. MTX 0.3 mg/kg/day IM	All 3
2. Act D 8–10 μg/kg/IV	daily for
3. Chlorambucil* 10 mg oral	5 days

* Alkylating agent with hematologic and GI toxicities.

defects or pulmonary compromise. In the Hammond et al series (23), only 30% maintained their reproductive potential. No incidence of obstetric complication or other disease processes could be attributed to prior treatment in these patients (23).

The follow-up of these patients is outlined in Table 12. Pregnancy is contraindicated for at least 1 year once remission is attained. Oral contraceptives are recommended as discussed previously. Oral contraceptives may be used continuously in patients having had a TAH to suppress the midcycle LH surge.

There is an extremely low likelihood of a relapse of disease after a *disease-free interval* of 1 year. Relapse will occur in approximately 1% of patients with normal gonadotropin levels for 1 year. The likelihood of a second molar pregnancy in a given individual is 4 or 5 times greater than that in the general population (21).

Conclusions

Despite numerous studies, many of which were done in recent years in Japan, China, Phillipines, Hawaii and other countries where trophoblastic diseases are highly prevalent, the histogenesis and natural history is still poorly understood. Perhaps the most challenging question which arises from the analogy between the invasive trophoblastic growth of normal gestation and the "out of control" growth of trophoblastic neoplasia is that regarding the breakdown of the mechanism providing the normal self-limiting nature of trophoblastic growth into the maternal host (12, 18). Gestation and tumor are the only situations in which the host tolerates the growth of an allogeneic tissue, which in both escapes the destructive immune reaction of the host. Gestational tumors represent a very special and particularly fascinating group of disorders, the understanding of which may shed light into both reproductive and carcinogenic processes.

The study of the spectrum of trophoblastic diseases should include the impact of genetic and developmental disorders in all five described entities of gestational trophoblastic diseases. Spontaneous abortions are the most common expression of faulty genetic coding, resulting in the elimination of a malformed conceptus as a form of natural selection. Partial and complete moles are less prevalent developmental anomalies with a potential for malignancy. Invasive moles and choriocarcinoma are the fortunately infrequent extreme forms of malignant growth of a maldeveloped conceptus. Although these are five separate entities, a certain continuity and a number of common denominators are obvious without, however, bearing the significance of a progression from one entity to the other.

The successful management of patients suffering from GTD includes early diagnosis, meticulous follow-up and prompt initiation of therapy, when indicated. With the advent of chemotherapy and a sensitive tumor marker, β-hCG, the outlook for malignant GTD has been completely changed. The prognosis of this once fatal group of neoplasms is excellent not only as far as the survival of the patients is concerned but also regarding their reproductive potential. It seems therefore appropriate to quote A. Hertig: "Gestational trophoblastic neoplasms are God's first cancer and man's first cure" (25).

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Hypertension in Pregnancy

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Hypertension during pregnancy may have devastating consequences for both the mother and her fetus. As several different conditions may result in increased blood pressure in pregnant women, the appropriate therapeutic approach is dependent on both the etiology and severity of the hypertension.

Classification

The accepted definition of hypertension in pregnancy is a rise in systolic and diastolic blood pressures in excess of 29 and 14 mm Hg, respectively, or values in excess of 139/89 mm Hg that are present on at least two occasions 6 hr apart (14).

Page and Christianson (38) have suggested that the hypertensive disorders of pregnancy be classified according to mean arterial pressure (MAP) and the presence or absence of proteinuria.

MAP is an index of cardiac work for it indicates the resistance to cardiac output. It can be calculated by adding the diastolic blood pressure to one-third of the pulse pressure. The mean arterial pressure offers the advantage of describing a physiologic function with a single numerical value. Mean arterial blood pressure changes as pregnancy progresses, with a characteristic fall during the second trimester (37). Page and Christianson have defined the upper range of normal for MAP during the second (MAP-2) and third (MAP-3) trimesters based upon perinatal mortality. MAP-2 is calculated as the average of all blood pressures taken during the 5th and 6th months of gestation. MAP-3 is derived from the highest two values separated by at least 6 hr during the third trimester. MAP-2 of 90 mm Hg or more and MAP-3 of 105 mm Hg or more are considered abnormal (38). Proteinuria is defined as more than 0.3 g/liter in a 24-hr urine specimen (quantitative +1) or more than 1 g/liter (quantitative +2) in a random specimen.

Edema has traditionally been considered to be one of the clinically necessary criteria for diagnosing preeclampsia. However, the Perinatal Task Force for the study of hypertension, proteinuria, and edema noted that 85% of all gravidas had edema at some point during gestation and that its presence alone did not change perinatal mortality. The association of edema and hypertension did not increase perinatal mortality above the risk level of hypertension alone (9). On this basis edema has been eliminated as a diagnostic criteria in the definition and classification of hypertension disorders of pregnancy. Edema was found, however, to increase perinatal mortality when associated with proteinuria. Page and Christianson (38) have proposed a classification of hypertension disorders of pregnancy based upon MAP-2, MAP-3 and the presence or absence of proteinuria (Table).

Chronic hypertension in an obstetrical patient is defined as sustained values of 140/90 mm Hg, or higher, that were present before the pregnancy and persist after the puerperium. Hypertension of this magnitude prior to 20 weeks of gestation (elevated MAP-2) is taken as presumptive evidence of its existence before conception. The definition does not distinguish between any of the diseases or syndromes associated with chronically elevated blood pressure. Among women in the reproductive years, the most common cause is essential hypertension, which is a disease that may vary greatly in its severity.

Gestational hypertension is defined as a normal MAP-2 followed by an elevated MAP-3 in the absence of proteinuria. The perinatal mortality in this group of patients is not elevated. Long-term follow-up studies indicate that there is a higher incidence of chronic hypertension in

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TABLE

Classification of Hypertensive Disorders of Pregnancy Based on MAP-2, MAP-3, and Proteinuria

Proteinuria in 3rd trimester	MAP-2	MAP-3 < 105	MAP-3 ≥ 105
Absent or less than 2+	<90	Normotensive	Gestational hypertension
	≥90	Borderline hypertension	Chronic hypertension
2+ or more	<90	Proteinuria, normotensive	Preeclampsia
	≥90	Proteinuria, borderline hypertension	Chronic hypertension plus preeclampsia

these patients. Pregnancy may act as a stress-causing gestational hypertension to occur in those prone to develop overt chronic hypertension in later life.

Preeclampsia is defined as an elevated MAP-3 and proteinuria in a patient with a normal MAP-2. Preeclampsia usually occurs after the 20th week of gestation, but it may become manifest earlier in association with trophoblastic disease, severe Rh sensitization, or α-thalassemia. It is primarily a disease of the first pregnancy carried to viability, and it appears with greater frequency as term approaches. When preeclampsia occurs in the multipara, there is often a predisposing factor, such as diabetes, Rh disease, multiple gestation, or antecedent chronic hypertension.

The clinical diagnosis of preeclampsia is often incorrect. McCartney (31) performed postpartum renal biopsies on 62 primigravidas known to be clinically normal in early and midpregnancy who developed hypertension, proteinuria, and edema in the third trimester. Characteristic glomerular lesions of preeclampsia were found in only 71% of cases. In the multipara, antenatal diagnostic accuracy is even less impressive. Chesley (4) states that the clinical impression of mild preeclampsia may encompass a variety of conditions including latent renal disease, preexisting chronic hypertension temporarily suppressed during midpregnancy and latent essential hypertension, in addition to true preeclampsia.

Preeclampsia can be classified clinically as being mild or severe. Severe preeclampsia is present if any of the following findings occur (Fig. 1):

1. Systolic blood pressure of 160 mm Hg or more, or diastolic blood pressure of 110 mm Hg or more, on at least two occasions (6 hr apart) at bed rest:
2. Proteinuria of 5 g or more in 24 hr (or 3+ or 4+ by semiquantitative assay);
3. Oliguria (500 ml or less in 24 hr);
4. Cerebral or visual disturbances such as altered consciousness, headache, blurred vision;
5. Pulmonary edema;
6. Marked hepatic dysfunction; and
7. Thrombocytopenia or other signs of disseminated intravascular coagulation.

Preeclampsia can also occur in a patient with chronic hypertension; this is termed superimposed preeclampsia and is diagnosed when a sharp increase in blood pressure (30 mm Hg sytolic or 15 mm Hg diastolic or more) and proteinuria occur.

Eclampsia is the occurrence of convulsions or coma in a preeclamptic patient. Eclampsia usually arises from severe cases of preeclampsia, but in several large series 25% of the cases were classified as mild prior to the convulsions. Other causes of seizures, such as epilepsy or cerebral vascular accidents, must be ruled out in these patients.

This classification of the hypertensive disorders of pregnancy is a retrospective one. Since proteinuria frequently occurs after the clinical onset of hypertension, the diagnosis of gestational hypertension, per se, cannot be made until after delivery. Likewise, eclampsia can occur with only mildly elevated blood pressure. Therefore, a uniform plan of management for patients with pregnancy-induced hypertension (PIH) is advisable to prevent maternal and fetal complications.

Pathophysiology

Although the cause of preeclampsia is unknown, vasospasm is a phenomenon central to the disease process. An increased pressor response has been demonstrated in patients destined to develop this condition. The infusion of angiotension II in nonpregnant women triggers a hypertensive response. Normal pregnant women are relatively resistant to the pressor effect of angiotensin II. The mechanism of this gestational angiotensin II resistance seems to be mediated by vasodilator prostaglandins since the administration of indomethacin to normal pregnant patients reduces the resistance to angiotensin II (15).

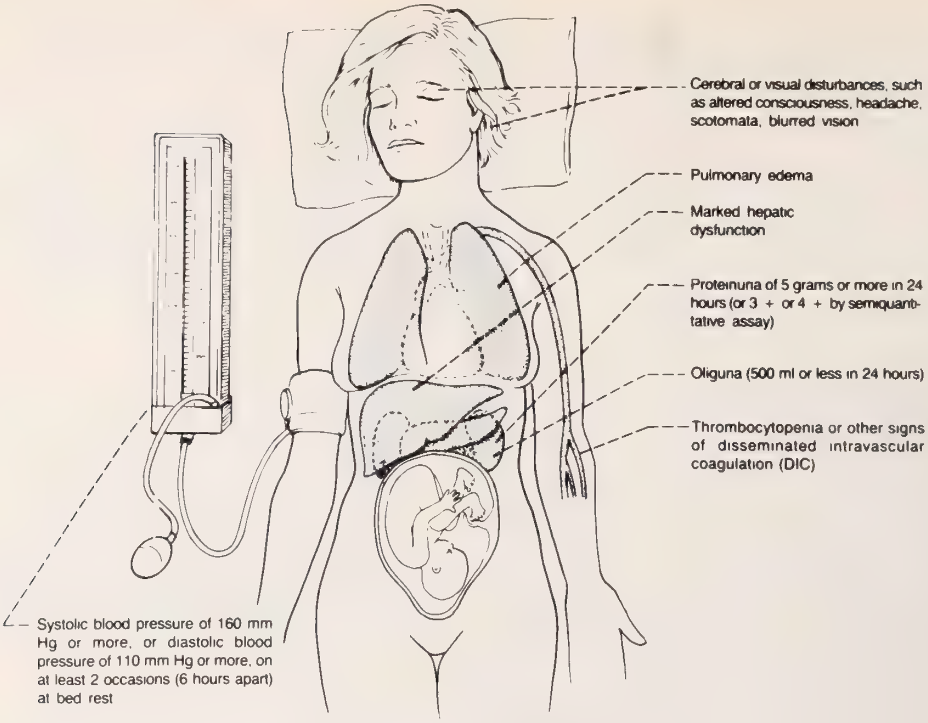

Cerebral or visual disturbances, such as altered consciousness, headache, scotomata, blurred vision
Pulmonary edema
Marked hepatic dysfunction
Proteinuria of 5 grams or more in 24 hours (or 3 + or 4 + by semiquantitative assay)
Oliguria (500 ml or less in 24 hours)
Thrombocytopenia or other signs of disseminated intravascular coagulation (DIC)
Systolic blood pressure of 160 mm Hg or more, or diastolic blood pressure of 110 mm Hg or more, on at least 2 occasions (6 hours apart) at bed rest

Fig. 1. Criteria for diagnosis of severe preeclampsia.

An attractive hypothesis for the pathophysiology of toxemia centers on prostacyclin, a potent vasodilator and inhibitor of platelet aggregation. A epoprostenol deficiency could explain both loss of angiotensin II resistance in pregnancy and the activation of platelets and coagulation factors in preeclampsia.

The combination of vasospasm and hypercoagulability can have many adverse affects on the uteroplacental circulation, kidneys, liver, hematopoietic system, respiratory system, pancreas, central nervous system, and eyes (Fig. 2).

Uteroplacental Circulation

Both vasospasm and platelet and fibrin deposition in the uteroplacental circulation lead to a reduction in uterine blood flow, as demonstrated by the rate of disappearance of radio-labeled sodium and the clearance of dehydroepiandrosterone sulfate. Decreased uteroplacental perfusion may result in intrauterine growth retardation, placental abruption, fetal distress, and stillbirth.

Kidneys

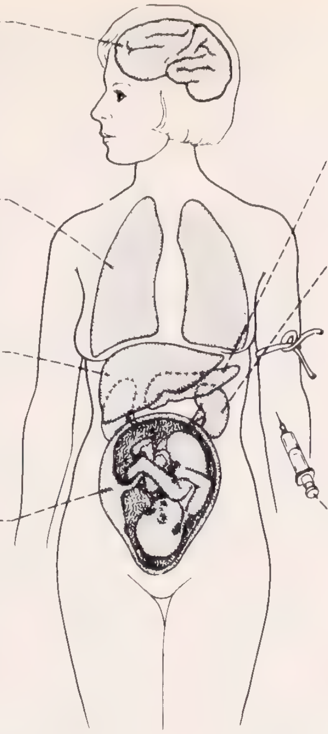
Vasospasm increases the afferent arteriolar resistance and decreases the glomerular perfusion pressure. This, coupled with a decreased intravascular volume, leads to decreased glomerular filtration, renal plasma flow, and filtration fraction—causing increases in BUN, creatinine and uric acid, and a decrease in creatinine clearance. Increased glomerular permeability, possibly due to local intravascular coagulation, is responsible for proteinuria. Glomeruloendotheliosis is considered by some to be the pathognomonic lesion of preeclampsia. With the use of immunofluorescence, fibrinogen-fibrin deposits can be demonstrated in the glomeruli. The lesion resolves spontaneously during the puerperium.

Liver

Elevations in SGOT and SGPT reflect hepatocellular damage. Mild elevation of bilirubin may be observed, but frank jaundice is exceedingly rare in uncomplicated preeclampsia. Liver biopsy has demonstrated periportal necrosis, and immunofluorescence studies have shown fibrinogen deposits in hepatic sinusoids. Subcapsular hemorrhage may become so extensive as to cause rupture of the capsule and massive intraperitoneal hemorrhage.

Hematopoietic System

A decrease in plasma volume can result in an elevated hematocrit. Traumatic, microangiopathic, hemolytic anemia can be produced by the passage of red cells through constricted vessels with intravascular fibrin deposits. Compensated hemolysis may be demonstrated by an elevated



CENTRAL NERVOUS SYSTEM

Neural hyperexcitability is common Hyperreflexia and severe headache may herald seizure. Hypertensive encephalopathy may occur. Intracranial hemorrhage is the main cause of death in pregnancy-induced hypertension

RESPIRATORY SYSTEM

Microthrombi may affect the pulmonary circulation. Adult respiratory distress syndrome may occur Pulmonary edema may complicate severe hypertension or fluid overload.

LIVER

Hepatocellular damage as a result of fibrinogen deposits in hepatic sinusoids may cause SGOT and SGPT elevations. Serum bilirubin may rise slightly. Subcapsular hemorrhage may be extensive

UTEROPLACENTAL CIRCULATION

Vasospasm and fibrin and platelet deposition may lead to reduction in uterine blood flow Diminished uteroplacental perfusion can cause fetal distress, stillbirth, or intrauterine growth retardation

EYES

Arteriolar spasm and hemorrhages, retinal edema, papilledema, retinal detachment, and central blindness may be present

PANCREAS

Ischemic pancreatitis is suggested by epigastric pain and an elevated urine amylase/creatinine ratio.

KIDNEYS

Vasospasm increases afferent arteriolar resistance and decreases glomerular perfusion pressure. In the presence of a decreased intra-vascular volume, there is a drop in GFR, RPF, and filtration fraction, resulting in elevated BUN, creatinine, and uric acid, and a decreased creatinine clearance. Proteinuria occurs as a consequence of increased glomerular permeability, likely due to local intra-vascular coagulation.

HEMATOPOIETIC SYSTEM

Elevated hematocrit, traumatic hemolytic anomia, elevated reticulocyte count, thrombocytopenia may be present. The last may be associated with abnormal liver function tests and intrauterine growth retardation.

Fig. 2. In preeclampsia, combination of vasospasm and hypercoagulability may have widespread critical effects on mother and fetus.

reticulocyte count. Thrombocytopenia is the most sensitive index of disseminated intravascular coagulation (DIC) in this condition. Elevated fibrin-split products indicate secondary fibrinolysis. Reduced fibrinogen levels reflect decompensated DIC, a rarer finding then compensated, chronic DIC in this disease. The presence of thrombocytopenia is often associated with abnormal liver function tests and evidence of intravascular coagulation (58).

Respiratory System

Pulmonary edema could result from severe systemic hypertension or inadvertent fluid overload. Adult respiratory distress syndrome has also been observed in the setting of severe preeclampsia.

Pancreas

Epigastric pain may occur in association with an elevated amylase:creatinine ratio, suggesting the presence of ischemic pancreatitis.

Central Nervous System

Neural hyperexcitability is associated with preeclampsia, as evidenced by hyperreflexia—considered, in conjunction with severe headache, a sign of impending seizure activity. The mechanism of seizure activity is unknown. A familial predisposition is suggested by a high incidence of EEG abnormality in relatives of eclamptic patients. Hypertensive encephalopathy may be partially responsible for the seizures seen in eclampsia. Intracranial hemorrhage is the main cause of death in pregnancy-induced hypertension.

Eyes

Arteriolar spasm can be seen on funduscopic examination. Other manifestations include arteriolar hemorrhages, retinal edema, papilledema, and retinal detachment. Transient central blindness has been reported during severe preeclampsia.

Antihypertensive Drugs

Diuretics

During most normal pregnancies, there is a gradual cumulative retention of between 500 and 900 mEq of sodium (30). This is distributed between the maternal extracellular volume and the products of conception and results in an increase in plasma volume. Sodium metabolism during pregnancy is controlled by multiple regulatory factors. These include increased glomerular filtration and renal perfusion rate as well as the opposing actions of progesterone and aldosterone. Circulating aldosterone levels are increased in the pregnant patient; however, she maintains the ability to respond to physiologic demands by further alterations in the production of this hormone. Experimental evidence suggests that normal pregnant women handle acute and chronic sodium loads similarly to nonpregnant patients, yet 80% of normotensive women develop dependent or generalized edema at some time during their otherwise uncomplicated gestations. While marked sodium retention and edema may occur in PIH, the relationship that this has with the etiology of PIH is unclear. Thiazide diuretics and furosemide are currently utilized in management of hypertension in pregnancy.

Thiazide Diuretics. Prolonged administration of diuretics to hypertensive patients results in reduced arterial pressure by decreasing total peripheral resistance. Thiazide diuretics inhibit electrolyte reabsorption in the distal collecting tubules resulting in an increase in sodium, chloride and potassium excretion, along with accompanying water. Initially, they cause a reduction in extracellular and plasma volumes, along with a concurrent decrease in cardiac output (CO). However, in 1–2 weeks plasma volume and CO return to normal levels, yet a reduction in peripheral resistance is maintained (49, 59). This effect may be secondary either to a direct action on the arteriolar smooth muscle or to changes of electrolyte concentration in its wall which could influence the tone or pressor responsiveness of the vessel (24). Because the autonomic reflex mechanisms essential for cardiovascular homeostasis are preserved, a proportional decrease in both systolic and diastolic BP occurs without any disturbances in regional circulation or orthostatic changes. Plasma renin increases, as a consequence of sodium depletion, often throughout the administration of the drug.

When patients become acutely toxemic, they have been demonstrated to have reduced plasma volumes (30). As administration of a diuretic further depletes intravascular volume, this may compromise the fetus by decreasing uterine blood flow, and place the mother in jeopardy should bleeding occur (2).

Gant et al (16) have demonstrated a reduced MCR_{DS} [metabolic clearance rate (MCR) of dehydroepiandrosterone sulfate (DS)] in 9 out of 10 pregnant patients studied on the 7th day of thiazide therapy. Approximately 40–50% of the total MCR_{DS} in pregnancy is secondary to placental conversion of DS to estradiol. Therefore, a reduction in this variable is believed to be a reflection of both uterine blood flow and the metabolic competence of the placenta. If the reduction in MCR_{DS} following thiazide therapy represents decreased placental perfusion, a strong case is made not to use diuretic agents in patients with PIH.

Complications of thiazide therapy during pregnancy include significant maternal electrolyte imbalances with severe hypokalemia and metabolic alkalosis (41), pancreatitis (32), thrombocytopenia (54), hyperglycemia (19), and hyperuricemia (8), as well as neonatal hyponatremia (1) and thrombocytopenia (50).

Furosemide. Furosemide is a potent diuretic which blocks the active reabsorption of chloride along with passive sodium reabsorption in the ascending loop of Henle. It can function even in the presence of significant renal insufficiency or volume depletion and is capable of causing severe electrolyte imbalance (3, 21). Therefore, it must be used with extreme caution in preeclamptic patients because of their contracted intravascular volume. The work of Gant et al (17) also suggests furosemide may decrease uterine blood flow. Except in patients with severe PIH and pulmonary edema, its use is rarely necessary. There have been no reported congenital abnormalities ascribed to the maternal administration of furosemide.

Drugs Affecting the Sympathetic Nervous System

Adrenergic impulses pass down the spinal cord to the paravertebral ganglia, where they are propagated across the synapse via acetylcholine. These impulses are conducted to their respective nerve endings within the vascular wall or myocardium, where norepinephrine is released. Norepinephrine stimulates α-receptor sites which cause vasoconstriction or β-sites which result in vasodilation. β-Stimulation also increases heart rate, contractility, and conduction velocity, while decreasing the refractory period at the atrioventricular node, but α-stimulation has little effect on the myocardium. In the brain the opposite effect is observed. α-Stimulation reduces BP, while β-stimulation increases it.

Adrenergic outflow from the brain causes increased renin release, which results in increased angiotensin and aldosterone production. A rise in aldosterone results in sodium retention, which increases the effectiveness of the action of catecholamines on vessels and the heart. A decrease in the adrenergic activity results in diminished vascular resistance which reduces hydrostatic pressure and permits influx of water from the extravascular compartment leading to an increased plasma volume. Intravascular volume depletion will augment the antihypertensive action of any drug that inhibits sympathetic activity (12).

Sympathetic blockers cause a decrease in heart rate (HR), vascular resistance and blood pressure. The normal reflex response to venous pooling is inhibited and can result in orthostatic hypotension and syncope in severe cases. This does not occur with agents which selectively block only β-activity.

Methyldopa and propranolol are currently utilized in the management of hypertension in pregnancy. Ganglionic blockers and rauwolfia alkaloids are inferior in both safety and reliability.

Methyldopa. The antihypertensive action of methyldopa is thought to occur through (*a*) stimulation of α-adrenergic receptor sites in the brain, (*b*) inhibition of dopa-decarboxylase, decreasing production of norepinephrine, (*c*) conversion of α-methyldopa to α-methylnorepinephrine, displacing norepinephrine, thereby causing less vasoconstriction, and possible (*d*) suppression of renin release (12).

The postural variation of blood pressure is much less marked with methyldopa than with guanethidine. Administration of methyldopa without the addition of a diuretic expands plasma and extracellular fluid volumes which reduces its antihypertensive effectiveness (24).

Side effects include drowsiness, depression, sodium retention, constipation, and lactation with high prolactin levels. After 6 months, a positive Coombs test develops in 20% of nonpregnant patients (12).

It is well suited for long-term use during pregnancy because it has little or no effect on cardiac output, and blood flow to the kidneys and uterus seems to be unimpaired (59). In a study by Redman's group (44) published in 1976, the outcome of 117 cases in which methyldopa was administered throughout pregnancy was studied. The authors concluded that the use of this medication for chronic maternal hypertension is safe for both mothers and their fetuses. A follow-up study (5) performed at the age of 7½ years showed the only significant difference between children of treated women and those of untreated controls was smaller head size in the sons of women who began taking methyldopa between 16 and 20 weeks gestation without a difference in intelligence quotient. They caution that treatment with this agent should not be initiated between 16 and 20 weeks gestation whenever possible.

Methyldopa has not proved useful during the management of hypertensive crises because, even when given intravenously, the onset of action is 4–6 hr. In addition, the intense vasospasm in severe PIH is more effectively treated with primary vasodilators.

β-Adrenergic Antagonists. The β-adrenergic antagonists lower blood pressure by several mechanisms: (*a*) β_1-stimulation of the heart is decreased, reducing HR, myocardial contractility, and CO; (*b*) unopposed α-stimulation in the CNS decreases BP; and (c) renin secretion by the kidneys is decreased (20).

Propranolol, timolol, and nadolol are nonselective β-adrenergic blockers. In addition, recently there has been the development of agents like atenolol and metoprolol which are selective β_1-selective adrenergic blockers (β_1-receptors are primarily in the heart; β_2-receptors are primarily in the peripheral vasculature, bronchi and uterus). Atenolol can be administered in single daily doses because of its longer plasma half-life (10, 11).

While these drugs can be effective in the treatment of hypertension, their effect is not additive. They may be interchanged in various clinical situations to achieve a decrease in specific side effects. In general, though, if one does not work, neither will another, assuming therapeutic doses are used. The practical benefits of using selective β_1-blockers are limited.

Propranolol, atenolol (55), metroprolol (52), and oxprenolol (13) have all been used in studies in obstetrical patients without remarkable differences, however, propronolol is by far the one most widely used in this situation.

Propranolol when given intravenously directly inhibits the rate and force of myocardial contractility rapidly decreasing both HR and CO. There is a transient rise in peripheral resistance caused by its inhibition of β-mediated vasodilatation, but this is reversed by its central action and by decreased kidney renin production in a few hours. Occasionally, propanolol can precipitate cardiac failure. Low doses, early in therapy, primarily in those patients who depend on β-stimulation to maintain cardiac function (3), are responsible for most of its significant cardiovascular problems.

In 2–10% of patients with no history of asthma, bronchospasm occurs. This drug is contraindicated in patients with compromised peripheral vasculature or Raynaud's phenomenon because of unopposed α-stimulation causing peripheral vasoconstriction. During acute stress, suppression of insulin release by β-blockage makes diabetics more susceptible to hyperglycemia, although insulin-dependent diabetics can become hypoglycemic because counterregulatory β-mediated glycogenolysis is blocked. In women with asthma, hypoglycemia, or peripheral vascular disease, selective β_1-blockers may be safe. Side effects of propranolol include insomnia, nightmares, hallucinations, depressions, paresthesias, ataxia, and dizziness (20). This drug given in conjunction with methyldopa may cause acute hypertensive episodes. Nies and Shand (35) have hypothesized that this is due to propranolol's potentiation of a metabolite of methyldopa, α-methylnorepinephrine.

There does not seem to be any maternal problems peculiar to the obstetrical patient taking propranolol. The drug easily crosses the placenta and is also secreted in breast milk. While no significant change in uterine blood flow was observed in studies on pregnant sheep (36), a significant reduction in umbilical blood flow was observed when given intravenously to the mother (42). Significant fetal side effects include growth retardation (22), neonatal hypoglycemia and bradycardia which persists during the first day of extrauterine life (18, 45). Difficulty in establishing spontaneous respiratory activity at birth in neonates whose mothers had been given intravenous propranolol immediately prior to elective cesarean section has been reported by Tunstall (56). He hypothesizes that the cervical sympathetic discharge which follows cord clamping is blocked by these agents.

In a retrospective study, Lieberman et al (29) found that the fetal outcome was worse in nine pregnancies in which maternal hypertension was treated with propranolol than in 15 similar cases in which other antihypertensive agents were used. Rubin (51), however, found three prospective studies which demonstrate that treatment of hypertension with propranolol during pregnancy may be beneficial to the fetus. After he analyzed studies involving other β-blockers and criticized methodologic flaws in the series with adverse results, he concludes that it is still not clear whether therapy with β-blockers specifically improves the outcome in patients with PIH. Additional large prospective trials with well-matched controls are necessary before it is clear that these agents offer advantages over other antihypertensive drugs for obstetric patients.

Clonidine. Clonidine is a sympathetic depressant whose mechanism of action is stimulation of α-adrenergic receptor sites in the hypothalamus and central nervous system but does not act on peripheral α-adrenergic receptors (12). While the renal release of renin is suppressed, there is no direct peripheral vasodilating effect.

Side effects include postural hypotension, sodium and fluid retention, bowel disturbances and, rarely, a weakly positive Coombs test. Occasionally, a symptomatic hypertensive crisis occurs upon abrupt withdrawal of the drug along with restlessness, tremor, headaches, and other symptoms suggestive of catecholamine release (12). A case has been published (61) of a woman with PIH who was given clonidine on the 5th postpartum day. The medication was inadvertently stopped after 2 days and a dramatic rise in BP to 250/190 mm Hg was noted along with tremor and palpitations. Attempts to adequately reduce the hypertension were unsuccessful, therefore clonidine was restarted in 3 days. A BP of 150/100 mm Hg, along with relief of her symptoms, was achieved without further hypertensive overshoot and the dose of clonidine was gradually reduced.

A case report has described a child born with Robert's syndrome (tetraphocomelia, cleft lip and palate, and failure to thrive) to a woman who took this drug throughout her pregnancy (53), but another report of its successful use in five Australian obstetrical patients (22) is noted. There are no published series that implicate clonidine as a teratogen but it has not been sufficiently evaluated to recommend its use in pregnancy. The same objectives can be achieved with more thoroughly studied agents.

Vasodilators. Vasodilating agents can decrease total peripheral resistance by more than 50% (25). The long-term effectiveness of this group is limited by: (*a*) reflex increase in sympathetic activity, which causes an increase in HR and CO which may be poorly tolerated by patients with limited cardiac reserve, and can diminish the hypotensive effect by 50–75%; (*b*) an increase in sympathetic discharge to the kidney increases plasma renin activity; and (*c*) sodium and water retention lead to increased extracellular fluid and plasma volume (25).

β-Blockers, which isolate the heart from excessive sympathetic stimulation and decrease the renal release of renin, prevent the first two side effects. With concomitant administration of a diuretic the third can be averted.

Severe chronic hypertension may require therapy with a drug from each of these three categories. The combination of a diuretic, β-blocker and vasodilator will control most degrees of hypertension and leave vasoconstrictor reflexes intact. This regimen is free from the other side effects of generalized sympathoplegia. Vasodilator therapy alone, however, is often all that is required in the acute hypertensive crisis. This is because after the BP is stabilized delivery frequently causes a resolution of the hypertension.

Hydralazine. Hydralazine is the hypertensive agent of choice for management of hypertensive crises in pregnancy. When this drug is not effective, sodium nitroprusside may be of value. Hydralazine directly relaxes arteriolar smooth muscle, decreasing vascular resistance. Resistance in the coronary, cerebral, splanchnic, and renal circulations is reduced more than that in skin and muscle. It has no direct action on the heart, and does not affect the autonomic nervous system, therefore orthostatic hypotension does not occur. Peripheral vasodilation and the subsequent hypotensive effect stimulates baroreceptors, causing an increased sympathetic discharge resulting in an increase in heart rate and cardiac output.

Sodium and water retention, increased by hydralazine, yield an expansion of plasma and extracellular fluid volumes, as well as weight gain, and edema formation. These are due to the reduction in arterial pressure caused by hydralazine and may be mediated by both the renin-angiotensin-aldosterone system and by direct renal mechanism (26). They are not the result of decreased renal blood flow or glomerular filtration rate as these are increased or unchanged.

Its metabolic conversion is by acetylation in the liver which is genetically determined by the activity of hepatic *N*-acetyltransferase. Consequently, slow acetylators will have higher serum concentrations than fast acetylators for any given dose.

For the treatment of hypertensive crisis, intravenous therapy is employed. Its onset of action by this route is approximately 15–20 minutes. The dose and frequency are variable but the initial dose should never exceed 20 mg. Pritchard and MacDonald (40) have recommended that in order to avoid the creation of hypotension in women with PIH, the initial intravenous dose should be 5 mg with additional 5- to 10-mg boluses being given every 20 min as needed. It is important to start with a low dose in order to avoid hypotensive overshoots in women who respond dramatically to the use of this drug, although 20-mg boluses may be necessary to maintain diastolic pressures between 90 and 110 mg.

Side effects include flushing, nasal congestion, headaches, dizziness, palpitations, angina attacks, and ECG changes of myocardial ischemia. They are related to either direct or reflex-mediated hemodynamic actions of the drug. A syndrome similar to lupus erythematosus has developed in people who are slow acetylators in doses exceeding 200 mg/day. Drug fever, rash, peripheral neuropathy, and blood dyscrasias may develop (26) very rarely.

The effect of hydralazine on the uteroplacental circulation is controversial. Ladner et al (27) observed decreased uterine blood flow in normotensive pregnant sheep, proportional to the reduction in maternal pressure after administration of hydralazine. Fetal pO_2 declined but fetal pH or cardiovascular parameters did not change. Gant and colleagues (17) reported a decrease in the MCR_{DS} by 6–59% in chronic hypertensive patients following the intravenous administration of hydralazine. Vink et al. (57) gave 12.5 mg dihydralazine intravenously over 4 min to 33 women with diastolic blood pressures (DBP) of 110 mm Hg or greater. Nineteen of these patients dropped their DBP to 70–90 mm Hg. Sixty-eight percent (13/19) delivered growth-retarded babies if there were fetal heart rate (FHR) decelerations, as opposed to 7% (1/14) of the group without them.

Woods and Brinkman (59), on the other hand, cite Page as showing that hydralazine increases uterine blood flow, and they state that propranolol effectively prevents this increase. Ring et al (47) demonstrated a statistically significant increase in uterine blood flow when hydralazine was given to pregnant sheep made hypertensive with intravenously administered phenylephrine. They also cite Brinkman and Assali as showing that hydralazine increases uterine blood flow in renal hypertensive pregnant sheep. No significant acid base changes in either mother or fetus were noted.

Most authorities believe that hydralazine given intravenously is the antihypertensive drug of choice in the management of a hypertensive crisis in pregnancy. It has demonstrated to adequately reduce the BP to acceptable limits in the overwhelming majority of cases of PIH. Without iatrogenically created hypotension, avoided by careful administration, it is well tolerated by the fetus.

Sodium Nitroprusside. The most potent and predictably effective agent available for the treatment of hypertensive emergencies is sodium nitroprusside (SNP). It dilates both resistance and capacitance blood vessels, being uniquely specific for vascular receptors. An effect on the autonomic or central nervous system has not been demonstrated. The preexisting state of cardiac performance best predicts the variable changes in CO and HR.

Nitroprusside must be given by carefully monitored constant infusion due to its virtually immediate action. The average adult dose is 3 μg/kg/min and should not exceed 800 μg/min (39).

There are no noticeable side effects if patients are not made hypotensive by excessive infusion. However, cyanide is liberated by the direct combination of nitroprusside with sulfhydryl groups in red blood cells and tissue and prolonged administration can lead to cyanide toxicity.

The placenta is readily permeable to SNP in animal models. Naulty et al. (34) found that five out of eight normotensive pregnant sheep required a steadily increasing dose of this agent in order to maintain a reduction in blood pressure of 20% for 1 hr. This was accompanied by a marked accumulation of cyanide in the mother with an even higher level in the fetus. The entire group of fetuses died. The authors hypothesized that the significant build-up of cyanide could be due either to rapid formation within the fetus or to a slower rate of detoxification and/or excretion. The therapeutic objective was obtained with a low rate of nitroprusside infusion in the remaining three sheep and their fetuses survived with low umbilical artery levels of cyanide. Uterine blood flow was not changed in either group. Ellis et al (7) infused sufficient amounts of SNP into pregnant sheep with norepinephrine-induced hypertension to return the BP to control levels without greater than 50 μg/liter of cyanide found in maternal or fetal blood. The therapeutic objective was achieved with low drug levels and without maternal or fetal toxicity.

The effects of SNP on uterine blood flow are controversial. Ring et al (47) found that SNP infusion did not change the reduction in uterine blood flow caused by phenylephrine-induced hypertension in pregnant ewes. Lieb et al (28) administered nitroprusside to both normotensive ewes and those with one-kidney hypertension. They noted a progressive decrease in uterine blood flow in both groups, averaging 35% and 25%, respectively, at the highest infusion rates. Ellis and colleagues (7), on the other hand, found that the administration of SNP to norepinephrine-induced hypertensive pregnant ewes caused a progressive increase in uterine blood flow.

SNP has been successfully used to create controlled hypertension for intracranial surgery during pregnancy (6, 28), and to stabilize the BP and reduce afterload prior to delivery in severe preeclampsia (46) in a small number. Its safety for the human fetus has not been adequately established. Some of the animal data are worrisome in that they suggest that cyanide toxicity could occur in the fetus while the mother is asymptomatic. Infusion of this drug may also cause a significant reduction in uterine blood flow. At the current time the use of SNP during hypertensive crises in pregnancy should be limited to those patients who do not respond to intravenous hydralazine. The patient should then be delivered as soon as possible.

Clinical Evaluation

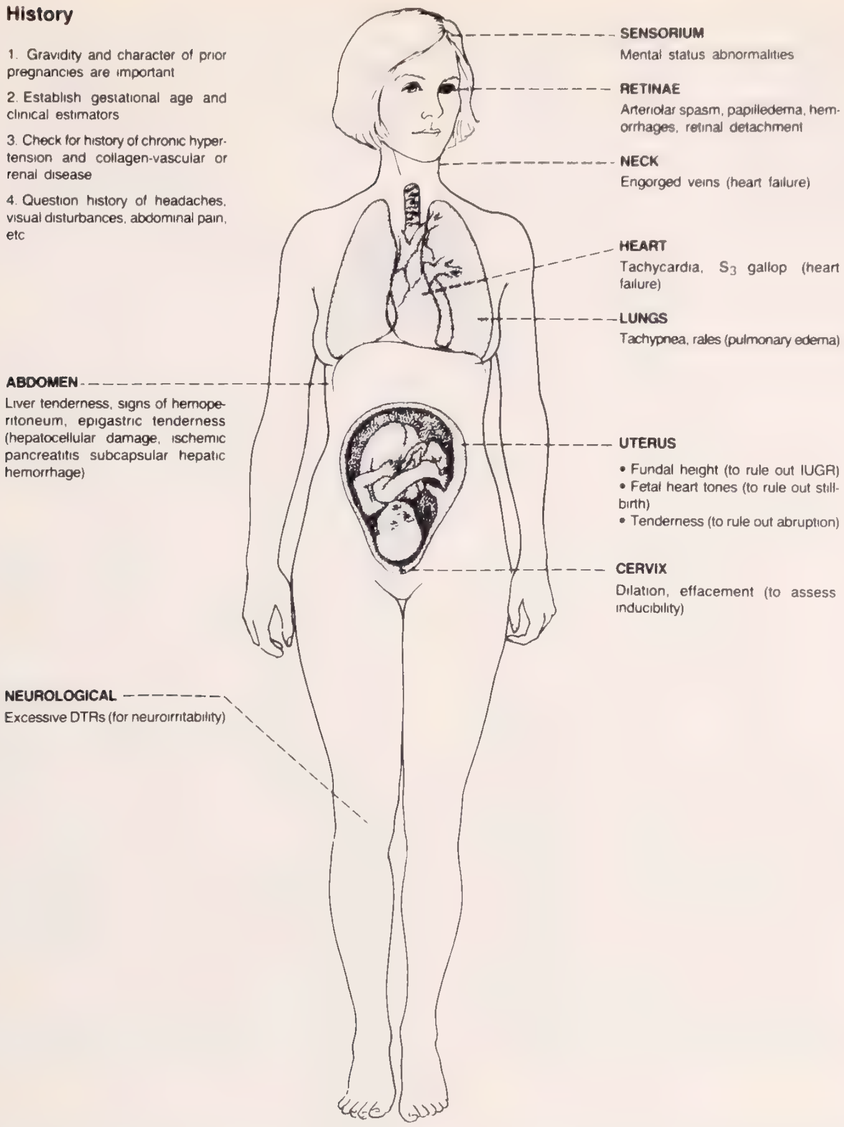
The clinical evaluation of the patient with PIH with regard to maternal history and physical examination are summarized in Fig. 3.

Management of Hypertension in Pregnancy

Chronic Hypertension

When a patient with chronic hypertension becomes pregnant, baseline renal function studies should be obtained. These include blood urea nitrogen (BUN), creatinine and uric acid, creatinine clearance, and 24-hr urinary protein excretion. These studies are repeated at regular intervals throughout gestation to be certain that maternal kidney function is not deteriorating. The gestational age of the fetus is confirmed by an ultrasound examination performed early in gestation. Fetal growth in utero is then followed with serial ultrasonic studies at 4-week intervals beginning at 28 weeks. Ideally, these examinations should include measurements of biparietal diameter (BPD), femur length (FL), head-to-body ratio (H:B ratio), estimated fetal weight (EFW), and assessment of amniotic fluid. If any of these parameters indicate suboptimal fetal growth, the patient is placed at bed rest on her left side, and fetal well-being is followed with periodic estriol determinations and weekly nonstress testing. When the fetus of a hypertensive woman shows objective evidence of asymetrical intrauterine growth retardation, we believe that the fetus should be delivered as soon as pulmonic maturity can be demonstrated by a lecithin:sphingomyelin (L:S) ratio of 2.0 or greater or positive phosphatidyl glycerol. In our opinion, intrauterine growth retardation (IUGR) in this setting reflects placental compromise, and the treatment of choice for the fetus is delivery with subsequent supportive therapy in a newborn special-care unit.

Many different therapeutic regimens for the pharmacologic control of hypertension in nonpregnant patients have been published. All of them, however, have recommended a "stepped-care program." This refers to initiating therapy with a small dose of an antihypertensive drug and then increasing its dose if necessary. Failure to



History

1. Gravidity and character of prior pregnancies are important
2. Establish gestational age and clinical estimators
3. Check for history of chronic hypertension and collagen-vascular or renal disease
4. Question history of headaches, visual disturbances, abdominal pain, etc

SENSORIUM
Mental status abnormalities

RETINAE
Arteriolar spasm, papilledema, hemorrhages, retinal detachment

NECK
Engorged veins (heart failure)

HEART
Tachycardia, S_3 gallop (heart failure)

LUNGS
Tachypnea, rales (pulmonary edema)

ABDOMEN
Liver tenderness, signs of hemoperitoneum, epigastric tenderness (hepatocellular damage, ischemic pancreatitis subcapsular hepatic hemorrhage)

UTERUS

- Fundal height (to rule out IUGR)
- Fetal heart tones (to rule out stillbirth)
- Tenderness (to rule out abruption)

CERVIX
Dilation, effacement (to assess inducibility)

NEUROLOGICAL
Excessive DTRs (for neuroirritability)

Fig. 3. Clinical evaluation (IUGR, intrauterine growth retardation; DTR, deep-tendon reflexes).

respond to this therapy requires the sequential addition of other therapeutic agents until the desired level of blood pressure is achieved. The initial dose of each drug should be as low as possible and then increased as necessary in order to attain the predetermined therapeutic goal.

While numerous medical regimens have been suggested in nonpregnant patients, they virtually all suggest beginning therapy with a diuretic agent (33, 48, 60). The use of diuretics in obstetrical patients remains a source of controversy. It is obvious that the complex changes in salt metabolism and fluid distribution during pregnancy should not casually be further disrupted. It is therefore inappropriate to prescribe diuretics as treatment for edema of pregnancy or as prophylaxis to prevent preeclampsia. In addition, these agents should probably not be used to treat the acute onset of hypertension in the second half of pregnancy because of concern about the consequences of a sudden reduction in intravascular volume.

In patients who are known chronic hypertensives, however, a convincing argument can be made for the rational use of diuretics during pregnancy. If these agents are being taken prior to conception, there is no solid evidence to suggest that reduced uterine perfusion results in fetal compromise. Furthermore, there are no convincing studies indicating that diuretic therapy initiated in the first half of pregnancy will compromise growth and development in utero. Work by Kaplan (23) indicates that when methyldopa is given concomitantly with a thiazide, the expected reduction in renal blood flow and glomerular filtration rate is minimized. This may also apply to uterine blood flow. In any event, the transient reduction in intravascular volume associated with the initiation of diuretic therapy is not maintained for more than a few weeks.

It is probably advisable to leave pregnant chronic hypertensive women on thiazide diuretic therapy if this has been started prior to conception. Reduction in circulating blood volume should not be an issue in these patients, and the diuretic allows maximal therapeutic latitude if additional drug therapy is required. If it becomes necessary to initiate therapy during the first half of pregnancy, a thiazide and methyldopa are given concomitantly.

Should a patient being treated with a diuretic alone require additional medication, the drug of choice is methyldopa because of the experience accumulated with the use of this drug during pregnancy. If further therapy is necessary, hydralazine is added to the regimen. Reserpine and guanethidine are not used because of annoying maternal side effects, and propranolol is not routinely employed because of its potential effects on the fetus.

Whenever diuretics are prescribed during pregnancy, careful observation of fetal growth is mandatory to be sure that a reduction in uterine perfusion is not causing nutritive deprivation. In addition, maternal serum electrolyte concentrations must be closely followed on a regular basis. Potassium supplementation is often necessary in order to maintain normokalemia, and the patient should be given a normal diet with only a "no salt added" restriction.

Pregnancy-Induced Hypertension

Clinical management of the patient with pregnancy-induced hypertension depends upon fetal maturity and severity of the disease.

Patients with mild preeclampsia, a mature infant, and a ripe cervix should be delivered. Without an obstetric contraindication, induction of labor is advisable. If the cervix is unripe or the baby is pulmonically immature, temporization is indicated.

Temporization of the patient may be conducted in an outpatient setting if there is mild hypertension (diastolic blood pressure less than 95 mm Hg) and no proteinuria, the patient is reliable, and none of the laboratory or clinical findings of severe preeclampsia are present. Bed rest in the left lateral position is the mainstay of outpatient management.

Mild sedation with phenobarbital is often used to facilitate adherence to a bed rest program. However, the efficacy of this modality has not been effectively demonstrated, and seizure prophylaxis is not reliable. The patient should be examined at least twice weekly to insure that there is no clinical or laboratory progression of the disease. Home monitoring of blood pressure may be of great adjunctive value. Fetal well-being and growth should be monitored with serial electronic fetal monitoring (EFM) and ultrasound examinations. Any evidence of fetal or maternal deterioration is an indication for hospitalization.

During hospitalization, patients are placed on bed rest, with monitoring of weight, blood pressure, urinary output, urine protein, retinal vessels, and deep tendon reflexes. Serial laboratory evaluations of CBC, platelet count, creatinine clearance, 24-h urinary protein, liver function, uric acid, BUN, creatinine, and fibrin split products are necessary. Serial nonstress tests and ultrasound examinations should be continued. With inpatient bed rest, improvement in blood pressure is frequently observed. Deterioration, with the onset of clinical or laboratory parameters of severe preeclampsia, is an indication for delivery.

Patients with severe preeclampsia should be delivered unless rapid improvement is observed. Hypertension above 180/110 mm Hg should be treated with parental hydralazine. A 5-mg initial dose can be given intravenously. If the desired hypotensive effect has not been reached in 20 min, the next dose can be increased by 5 to 15 mg. Once the blood pressure has been lowered into the range of 140–160/100–110 mm Hg, intermittent bolus therapy or administration of a continuous hydralazine drip may be utilized.

Cesarean section is not necessary in most cases of PIH unless fetal distress, life-threatening maternal complications or obstetrical indication are present. Vaginal delivery avoids the risks associated with anesthesia and abdominal surgery with the attendent problems of blood loss and the implications for future deliveries if a cesarean section is performed. Induction is often successful with patients with PIH, even if the cervix is initially unfavorable. Careful fetal and maternal monitoring is mandatory. Epidural anesthesia may be utilized after blood pressure has been stabilized and satisfactory urine output is present in those cases where there is no fetal distress.

Magnesium sulfate ($MgSO_4$) should be started to prevent convulsions. A 4-g loading dose is followed by infusion of 1–2 g/hr (titrated against deep tendon reflexes). A Foley catheter should be inserted to follow hourly urinary output. Adjustment in the magnesium infusion rate may be necessary if the urinary output drops below 50 ml/

hr. Respiratory depression and arrest may occur if levels of 10–15 mEq/liter or above are present. Calcium gluconate (10 ml of a 10% solution) should be administered to reverse magnesium toxicity. After delivery, $MgSO_4$ should be continued for 24 hr in cases of severe hypertension and may be required for longer periods of time.

As hypovolemia has been documented to commonly occur in conjunction with PIH (43), careful monitoring of fluid input is essential. If oliguria or evidence of hemoconcentration is present, volume repletion is indicated. Urine output should be maintained at 30 ml/hour or greater. We recommend the administration of 2000 ml of crystalloid solution over a 2-hour period if necessary. If there is no improvement in urinary output, hydration with monitoring by a central venous pressure line or Swan-Ganz catheter is indicated. In this setting, colloid solution administration may be necessary in order to maintain urinary output.

During the postpartum period, a normal redistribution of fluid from the extravascular compartment occurs. Patients aggressively hydrated in the antepartum period can go into pulmonary edema after delivery. The infusion of crystalloid solution should be slowed to a rate of 75 ml/hr and the patient frequently checked for the development of tachypnea, tachycardia, cyanosis, or ausculatory evidence of pulmonary edema. A urinary output of 30 ml/hr is satisfactory and therapy is not necessary to increase it above this level. If urinary output is decreased, 20–40 mg of furosemide can be administered intravenously.

Eclamptic patients must be protected during a seizure. A padded tongue blade should be inserted and an airway maintained. The patient should not be forcefully restrained since this may lead to fractures. Oxygen should be administered and the airway cleared of secretions. Magnesium sulfate should be started immediately in the manner previously described.

Recurrent seizures unresponsive to $MgSO_4$ can be treated with intravenous sodium amobarbital or diazepam. Vaginal delivery may be attempted after stabilization of the patient. Hypertension can be controlled with hydralazine as previously described.

Conclusion

Hypertension during pregnancy may cause significant fetal and maternal morbidity in addition to increasing perinatal mortality. Optimal care requires that the etiologic diagnosis be as accurate as possible and that maternal renal function be thoroughly assessed. The fetus is jeopardized when placental function is compromised, and therefore its growth in utero should be followed closely. The therapeutic approach to hypertensive obstetrical patients depends on the chronicity as well as the severity of the condition. A rational use of available antihypertensive agents requires an understanding of their pharmacologic properties as well as the pathophysiology of the different disorders seen in pregnancy. With treatment that adheres to sound principles based on this understanding, the obstetrical patient with elevated blood pressure can often have a safe pregnancy and deliver a healthy baby.

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Thyroid Disease in Pregnancy and the Postpartum Period

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The evaluation and management of thyroid function and dysfunction in pregnancy imposes a challenge to the combined efforts of the thyroidologist and obstetrician. Thyroid disease is so prevalent in the population that the combination of pregnancy and thyroid disease is commonplace. Furthermore, the recent reports that postpartum thyroid dysfunction may be more common than first suspected has aroused great interest in the relationship between thyroid disease and pregnancy. One of the earliest descriptions of hyperthyroidism, by Parry (95) in 1825, described a large swollen thyroid gland in a woman some 3 months postpartum: "The carotid arteries on each side were greatly distended; the eyes were protruded from their sockets, and the countenance exhibited an appearance of agitation and distress . . . which I have rarely seen equalled." Treatment of such thyroid disorders obviously requires an awareness of many fundamental concepts since they accurately predict the effects of disease and therapy on both the mother and child.

Normal Thyroid Physiology

Feedback Control of Thyroid Function

The thyroid gland accumulates iodine from the circulation in an active, energy-requiring process against a concentration gradient, the extent of which is regulated primarily by thyroid-stimulating hormone (TSH) and plasma iodine concentration (for review, see DeGroot and Stanbury (36)). Iodine is organified by a peroxidase enzyme system. Tyrosine rings within 19 S thyroglobulin molecules are progressively iodinated and coupled to form the thyroid hormones triiodothyronine (T_3) and thyroxine (T_4). T_3 and T_4 generally exist within the thyroid gland in a ratio of 1 to 10 or 1 to 20, respectively. These molecules are hydrolyzed off the thyroglobulin molecule and released concomitantly into the circulation. All steps are accelerated by pituitary TSH. This glycoprotein hormone binds to specific thyroid surface receptors and activates cyclic AMP (33). The pituitary "set point" is influenced by hypothalamic TSH releasing hormone (TRH) which increases TSH release and synthesis. Conversely, T_4 and T_3 exert negative feedback directly on the pituitary by causing decreases in TRH receptors and the production of an inhibitory protein, thus reducing the TSH response to TRH. Hence, a classic negative feedback loop occurs with TRH acting to modify the set point.

The Thyroid Hormones

Once released into the circulation, T_4 is 99.5% bound to carrier proteins, hence only 0.5% is in the free and active state. Thyroid binding globulin (TBG), an inter-α-globulin, binds 60–70% of the circulating T_4 at a high affinity and relatively low capacity, while thyroid binding prealbumin binds 20–30% of the circulating hormone with a lower affinity but greater capacity. The remaining 10% of bound circulating thyroid hormone is associated with serum albumin. Occasionally individuals have aberrant binding proteins which require careful evaluation (71, 112).

T_3 is 4–5 times more potent than T_4 on a molar basis. The affinity of T_3 for TBG is $\frac{1}{10}$ that of T_4 and the circulating free T_3 level is, therefore, less affected by alterations in the thyroid binding proteins. A small amount of T_3 is secreted directly from the thyroid gland, especially in situations of

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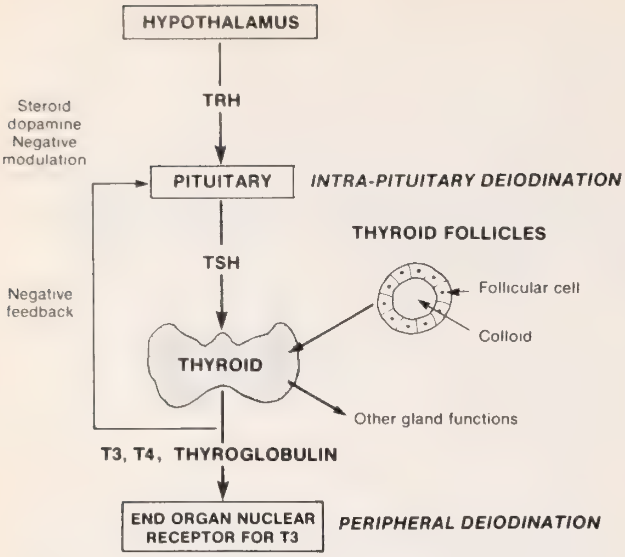
HYPOTHALAMUS
TRH
Steroid dopamine Negative modulation
PITUITARY
INTRA-PITUITARY DEIODINATION
THYROID FOLLICLES
TSH
Negative feedback
Follicular cell
Colloid
THYROID
Other gland functions
T3, T4, THYROGLOBULIN
END ORGAN NUCLEAR RECEPTOR FOR T3
PERIPHERAL DEIODINATION

Fig. 1. Outline of hypothalamic-pituitary-thyroid axis with its classical feedback network.

iodine deficiency. However, 80% of circulating T_3 is derived from peripheral deiodination of T_4 by a 5′-monodeiodination occurring in liver, muscle, and a variety of other tissues. Thus T_4 may be a secretory product which serves as a precursor or "prohormone" for the biologically active T_3. Occasionally true T_3 hyperthyroidism in the presence of normal T_4 levels is seen. This occurs most commonly in the presence of relative iodine deficiency seen in certain populations and after withdrawal of antithyroid drugs where intrathyroidal iodine may be low (see under "Antithyroid Drugs"). T_4 can also be monodeiodinated to an inactive 3,3′,5′-reverse T_3. Metabolic disturbances frequently result in preferential deiodination to reverse T_3 and together with its decreased clearance result in the low T_3 syndromes commonly seen in hospitalized patients.

Thyroid hormones may be bound by cell membranes and then transferred to the cell nucleus where they exert their effects by accelerating mRNA transcription and protein synthesis. The importance of mitochondrial and other extranuclear binding sites is uncertain (48).

Thyroid Function in Pregnancy

The Thyroid Gland

In the pregnant female the thyroid gland responds to a number of physiological alterations:

1. Iodine turnover is increased secondary to a higher glomerular filtration rate and renal iodine clearance. This causes a decrease in the proportion of iodine accumulated by the thyroid gland and may be responsible for some degree of organ hypertrophy (38) (see below).

2. Estrogen causes increased TBG synthesis from the liver and more T_4 is bound to circulating protein. Total circulating thyroid hormone is increased but the free and biologically active T_4 is normally maintained within the eumetabolic range (Table 1). Metabolic clearance of T_4 and T_3 during pregnancy reaches a new steady state, the metabolic clearance rate (MCR) of T_4 is being measured at 97 μg per day like the nonpregnant rate of 90 μg per day (48).

3. The TSH response to TRH has been reported to be increased during the 16th to 20th week of pregnancy (23), presumably as a function of both estrogen effects on the pituitary and possibly elevated endogenous TRH (10).

4. Human chorionic gonadotropin (hCG) has intrinsic thyroid stimulating ability due to its low affinity interaction at the TSH receptor (26, 35). Recent studies have indicated small elevations of free thyroid hormone (still within the normal range) corresponding to the time of peak hCG titers early in pregnancy (60, 130). Physiologically, this may be of little consequence, but in hydatidiform mole or choriocarcinoma, hyperthy-

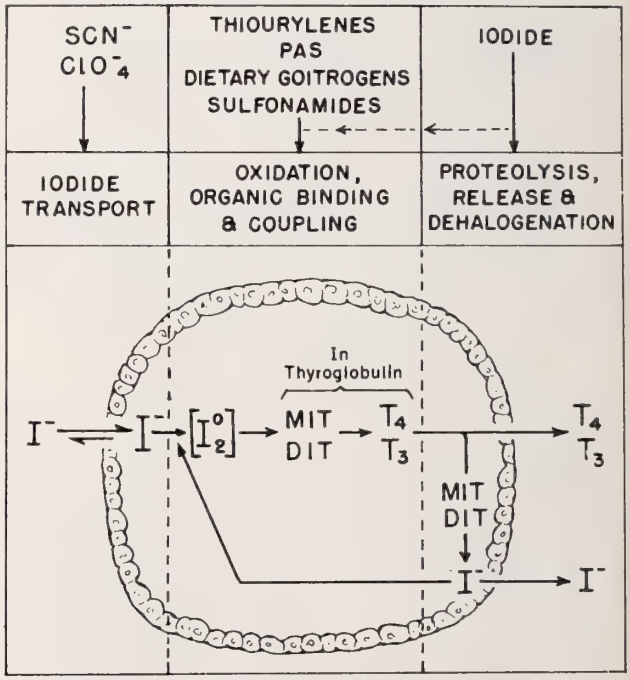
SCN⁻
ClO₄⁻
THIOURYLENES
PAS
DIETARY GOITROGENS
SULFONAMIDES
IODIDE
IODIDE TRANSPORT
OXIDATION, ORGANIC BINDING & COUPLING
PROTEOLYSIS, RELEASE & DEHALOGENATION
In Thyroglobulin
I⁻
I⁻
[I₂⁰]
MIT
DIT
T₄
T₃
T₄
T₃
MIT
DIT
I⁻
I⁻

Fig. 2. Thyroid hormone synthesis. Intrafollicular lumen represents interstitial compartment rather than true follicle lumen. Also shown are major inhibitors of the several steps in hormone biosynthesis. In addition, lithium acts like iodide, as an inhibitor of proteolysis and release. From S. Ingbar and S. Woeber, in R. H. Williams (ed.): Textbook of Endocrinology, Ed. 6, W. B. Saunders, Philadelphia, 1981.

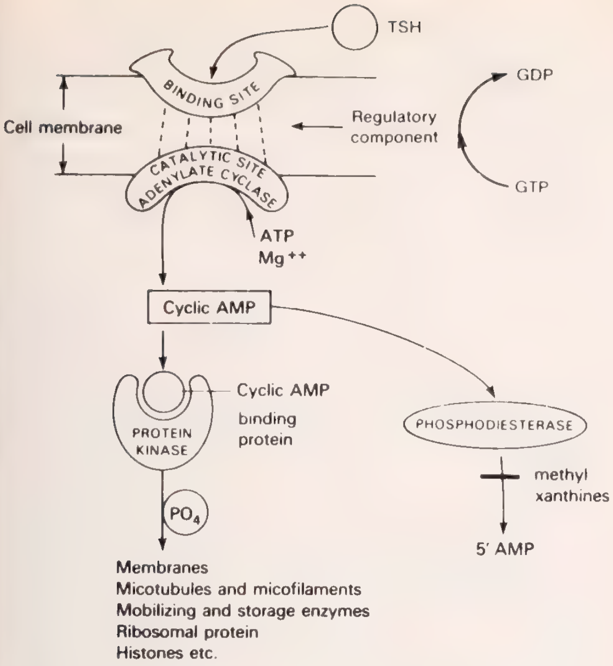

Fig. 3. The TSH receptor/adenylate cyclase system.

roidism secondary to hCG stimulation may result (35, 89).

Placental Transfer

The placental barrier in pregnancy effectively screens the fetus from many alterations in maternal thyroid status because TSH and TBG do not penetrate. Only a small amount of T_4 crosses the placenta. T_3, though more permeable, is considered to cross only minimally in a sulfated form which is metabolically inactive (108). Certain thyroid hormone analogs have been synthesized (e.g. dimit) which do show biological activity and much improved placental transfer. However, the difficulty in monitoring the fetal impact of such therapy is likely to restrict the use of such an approach in man. Given the large pool of unsaturated maternal TBG in pregnancy, the gradient in transplacental passage of thyroid hormones may favor transport from fetus to mother (127). Under pathological conditions, the fetus may be exposed to alterations in thyroid function by the passage of nonphysiologic molecules across the placental barrier. IgG antibodies, including thyroid stimulating antibodies (TSAb), the etiologic agent of Graves' disease (88), traverse the placenta, as do iodine, TRH, antithyroid drugs and β-blockers including propranolol (21, 31, 50).

Immune Function

Much of thyroid disease seen during the childbearing years is autoimmune in etiology (34). The fact that normal immune surveillance is diminished in pregnancy has been well documented (see Immunology in Pregnancy). Depressed cellular immunity has been characterized by decreased skin graft rejection, reduced PHA induced immunocyte stimulation, and a lower response to PPD and dinitrochlorobenzene (DNCB) in skin testing (53). Such diminished immune function may be partially related to changes in cortisol levels, hCG or other circulating factors in pregnancy and to the transfer of such immune suppressor factors from the fetus to the maternal circulation (125). Diminished immunosurveillance may clinically be associated with declining goiter size, decreased thyroid antibody titers, reduced circulating peripheral lymphocyte function, and with partial or complete autoimmune thyroid disease remission in pregnancy (9, 109). The practical implications of this concept are clear:

1. If thyroid autoimmune disease severity is altered, medical therapy may require adjustments during pregnancy.
2. Rebound of autoimmune disease with elevated antibody titers in the postpartum period may lead to either transient or permanent abnormalities in thyroid function.

Fetal Considerations

Fetal maturation of the hypothalamic pituitary thyroid axis (56) must be considered in the management of maternal thyroid disease (Fig. 4). After development as an out-pouching of gut endoderm and migration from the buccal area into the neck, at 12 weeks the fetal thyroid gland has developed a normal histological appearance, is able to organify iodine, and secrete thyroid hormone. Near midgestation, pituitary TSH has increased into the physiological range and may exceed maternal levels. Other parameters of pituitary function also appear by this time as evidenced by growth hormone and prolactin levels (58) both of which are measurable during the first trimester and rise progressively toward term. There is a concomitant increase in fetal TBG production, but free T_4 values may be higher than expected suggesting increased biological activity of TSH. Near term values of free T_4 may exceed the maternal range (Table 1). By contrast, total T_3 is consistently low, with elevated reverse T_3. Metabolic clearance studies of fetal sheep T_4,

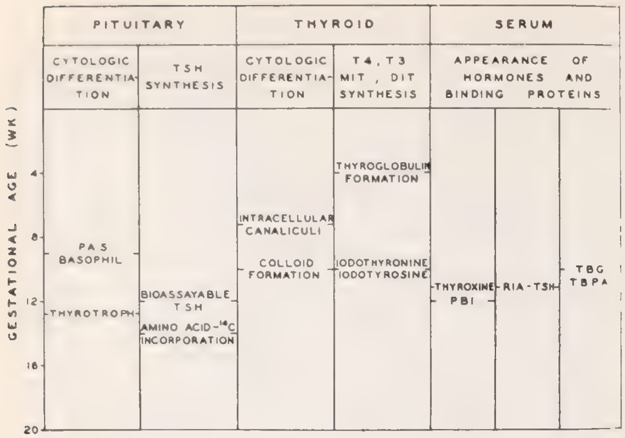

Fig. 4. Histological and functional differentiation of human thyroid. From A. H. Greenberg et al.: Journal of Clinical Investigation, 49:1790, 1970 (56).

T_3 and reverse T_3 suggest that immaturity of the 5′-deiodinase enzyme may be responsible for this phenomenon (29). Despite the reduced T_3, the fetus is eumetabolic by clinical assessment. Following delivery there is a rapid transient surge in TRH, TSH, T_4 and T_3, all of which return to the normal adult range within 3–4 days (Table 2).

Clinical Aspects

The normal thyroid gland has been said to both enlarge and remain unchanged (32, 73, 115) in healthy pregnant females. The incidence of goiter varies geographically, perhaps in relation to ambient iodine supply. The presence of thyromegaly may imply a primary thyroid disorder rather than the result of pregnancy alone. Studies of pregnant women at postmortem demonstrated increased cellular hypertrophy and vascularity of the thyroid (115) but the presence of gross glandular hypertrophy remains in dispute. The recent demonstration of estrogen receptors in thyroid tissue suggests the possibility of a direct impact on the thyroid follicular cell.

Normal pregnant subjects mimic the hyperthyroid state by appearing nervous, having a resting tachycardia, having smooth, moist, slightly diaphoretic skin, with warm, soft erythematous palms and clinically apparent systolic cardiac murmurs. There is cutaneous vasodilatation and the basal metabolic rate is elevated because of increased oxidative metabolism in pregnancy. Careful biochemical evaluation of thyroid function is, therefore, often more decisive than clinical evaluation.

Thyroid Function Testing in Pregnancy

The availability of accurate measurements for T_4, T_3, TBG (or T_3 resin uptake) and TSH by radioimmunoassay make the calculation of thyroid function precise. The chemical diagnoses of hyper- and hypothyroidism are now made with little difficulty, even when clinical signs are conflicting. The ratio of T_4 to TBG (or a resin binding test) correlates well with free T_4 measurements and, in many cases, is adequate for diagnosis (Table 3). It is important to note that the T_4: TBG ratio decreases during pregnancy for uncertain reasons, perhaps because of inhibition of T_4 binding to the carrier protein. Free thyroid hormone analysis by equilibrium dialysis is expensive, time consuming, and not readily available in most centers. It remains, however, the only direct measurement of the T_3 and T_4 concentrations available to the tissues. In the case of borderline elevations of calculated free T_4, certain other ancillary measures are unwise in pregnancy; for example, thyroid scanning and measurement of radioactive iodine uptake. A T_3 radioimmunoassay (RIA) remains the most helpful widely available secondary investigation (110). TRH testing, which would normally be performed under such circumstances, is not recommended in pregnancy because it crosses the placenta and also may be associated with smooth muscle, hence uterine, contractions. While reports of fetal damage have not been reported, we feel its use is rarely warranted. Since minimal or mild hyperthyroidism is not felt to be dangerous in itself, repeat testing and clinical observation prior to the institution of therapy is felt most advisable.

Hypothyroidism is usually much simpler to diagnose because of the great efficacy of TSH levels as a monitor of thyroid hormone deficiency. In hypothyroidism secondary to thyroidal disease the TSH level is always raised and further stimulation with TRH is not indicated. Total T_4 or a

TABLE 1

Thyroid Function Tests in Normal Pregnancy

	T_4:TBG ratio in normal pregnancy (mean ± SD)		
Variable	Female controls	2nd trimester	3rd trimester
Number	100	21	80
T_4 (μg/100 ml)	9.0 ± 2.5	13.1 ± 2.6	13.5 ± 2.6
TBG (μg/ml)	22.8 ± 4.9	41.8 ± 6.0	41.7 ± 5.6
T_4:TBG ratio	4.2 ± 0.65	3.2 ± 0.57	3.2 ± 0.58
T_3	120 ± 12	188 ± 42	210 ± 25

Normal ranges are required for each laboratory.

TABLE 2
Thyroid Functions Tests in Neonatal Period

	Approximate values for thyroid function tests in infants		
Tests	Newborn cord blood	3–5 days	2 week–3 months
T_4 (μg/dl)	12	15	11
	6–17	9–20	7–15
T_3 (ng/dl)	50	130	160
	10–90	50–210	160–240
TSH (μU/ml)	9.5	6	4
	1–20	U–20	U–10

From D. A. Fisher and G. N. Burrow (48).
Values as mean and 95% range; U is undetectable.

derived T_4 index is normally low or in the low normal range. Free hormone levels are poor indicators of reduced thyroid function and are not indicated (131). Similarly, total T_3 levels are of little help in detecting thyroid failure and should not be requested.

Fundamentals of Autoimmune Thyroid Disease

Because the majority of pregnant patients with thyroid disease have Graves' or Hashimoto's disease it is important to understand the etiology of these common diseases. Two principal forms of immunological influence on thyroid function are known: stimulation by stimulating antibodies and destruction by antibodies capable of destroying cells. Hence we have a spectrum of disease from hyperthyroid Graves' patients to those in gross thyroid failure due to autoimmune thyroiditis (Hashimoto's disease) (Fig. 5). The presentation of disease in patients appears to depend upon the balance between these influences.

Evidence for the association of disordered immunity and thyroid disease is based on the pathological nature of the thyroid lesions, the presence of a variety of thyroid autoantibodies in the circulation and within the thyroid tissue itself, and by the association of thyroid disease with other autoimmune abnormalities. It is important to be aware of the data indicating the primary nature of the immune abnormalities rather than their being secondary to some other thyroid abnormality. In certain situations, for example subacute thyroiditis, thyroid autoantibodies are detected in transiently increased titers and fade with decline of the disease. In contrast, in autoimmune thyroid disease, autoantibodies may predate obvious tissue changes and both destructive and stimulating antibodies are capable of tissue effects in vitro (1, 65) and in vivo (2, 30). Furthermore, the failure to develop simple animal models which closely resemble human disease indicates the uniqueness of these disorders to man.

Thyroid Stimulating and TSH Receptor Antibodies

Sera from patients with hyperthyroid Graves' disease contain what we now call thyroid-stimulating antibodies (TSAb) discovered by Adams and Purves (1) in 1956 in the form of long acting thyroid stimulator (LATS) and which can be measured by a variety of in vitro bioassays such as the thyroid slice or thyroid cell techniques (61, 93). Of untreated patients, 70–85% demonstrate easily measurable TSAb levels, and administration of Graves' immunoglobulins intravenously induces thyroid stimulation in human volunteers (2). Hence TSAb is the primary causative agent of Graves' hyperthyroidism and its presence is diagnostic of the disease (Fig. 6).

Many IgG preparations from patients with TSAb also inhibit the binding of radiolabeled TSH to thyroid cells or isolated TSH receptors (44, 78, 111). This TSH binding inhibition (TBI) appears to be secondary to the presence of TSH receptor antibodies. It may be that TSAb and TBI activity are one and the same thing in most patients. However, it is now clear that not all TSH receptor antibodies measured by TBI activity are necessarily able to stimulate the receptor site. Many are able to block TSH action at the receptor, therefore acting as TSH antagonists or partial agonists (40). Recent production of human mononclonal antibodies from patients with Graves' disease indicates that the ratio of stimulating to inhibiting activity may be very variable within a single clone of cells (121).

Practically speaking, the TSAb bioassays are very much more difficult and expensive to perform than the measurement of TBI activity. Hence in hyperthyroid patients TBI is the measurement of choice. However, if the patient is not

TABLE 3
Appropriate Thyroid Function Tests in Relation to Suspected Diagnosis

	Thyroid function test strategy		
Suspected disorder	Primary test	Secondary test	Antibody confirmation
Hyperthyroidism	T_4:TBG or resin uptake	T_3	TSAb/TBI
Hypothyroidism	T_4:TBG or resin uptake	TSH	Anti-hTg Anti-M

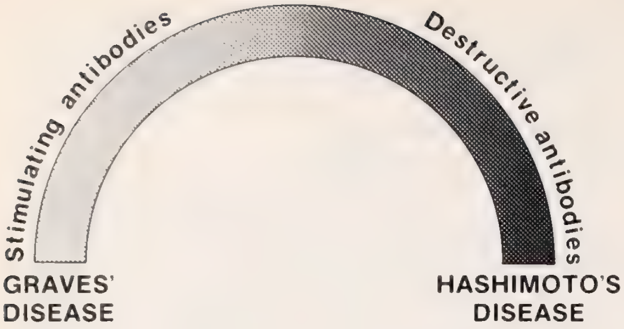

Fig. 5. Spectrum of autoimmune thyroid disease.

hyperthyroid, then some assessment of bioactivity may be helpful.

Thyroglobulin Antibodies

The pathogenetic role of antibodies to human thyroglobulin (hTg-Ab) has been inferred by their correlation with lymphocytic infiltration and their high titer in autoimmune thyroiditis (Hashimoto's disease) (103, 132). Antibody to hTg would clearly have access to antigen on the surface of the thyroid cell and has the potential to initiate thyroiditis as demonstrated in animal models (30). hTg-Ab are easily measured by tanned red cell hemagglutination, radioassay, or enzyme-linked immunosorbent assay (ELISA) systems (49, 84, 86, 104) and such tests are widely available. Of the general population, 2% have hTg-Ab by hemagglutination but titers are commoner and higher in patients with both Graves' and Hashimoto's diseases being found in approximately 15–20% and 70%, respectively.

Thyroid Microsomal Antibodies

Many patients with autoimmune thyroid disease demonstrate high titers of antibody to a sonicated 80,000 g fraction of thyroid homogenate. Such microsomal antibodies are readily measured using this crude antigen in hemagglutination, radioassay and ELISA techniques (18, 86, 104). Of people with M-Ab, 70–80% have evidence of thyroid disease (119) and such antibodies show a better correlation with thyroiditis and elevated TSH in the general population than hTg-Ab (120, 132). The nature of the antigen remains uncertain, but it is thought to be a mixture of both surface and intracellular antigens (47). Up to 7% of the population have M-Ab by hemagglutination and 20% by radioassay, and such prevalence increases with age (119). Over 90% of patients with Hashimoto's and 50% with Graves' disease have easily detectable M-Ab, the titers often being extremely high in Hashimoto's thyroiditis.

Immunocyte Function in Thyroid Disease

Direct production of thyroid autoantibodies in vitro has not deteted any convincing abnormality in T-suppressor cells in patients with autoimmune thyroid disease (16, 83). Evidence for and against nonspecific decreases in the total circulating T-suppressor cells of such patients has been reported (13, 25, 114, 123), but the functional correlate of such findings is not yet available. None of the in vitro systems for measuring thyroid autoantibody secretion have been entirely antigen-specific, requiring a mitogen to be present, although the new ELISA techniques are now sensitive enough for such studies to be performed. It is unlikely that changes in specific T cell regulation would, therefore, have been revealed by earlier approaches. Hence, many critical questions remain in order to understand why particular individuals have the propensity to secrete thyroid autoantibodies and why some such individuals progress to thyroid disease. What may be even more preplexing is why other individuals with thyroid autoantibodies remain euthyroid for many years. It would appear to us that the principal abnormality may lie within the B cells themselves (126) since an abnormal clone must be inherited and allowed to survive, perhaps because of impaired immunosurveillance or resistance to normal control mechanisms. The important modulators of such a progression remain to be determined.

Cell-Mediated Immunity in Thyroid Disease

The precise role of cell-mediated, rather than humoral, immunity in the etiology of thyroid disease in unclear (66). The interaction of immunogen with sensitized T cells causes the release of nonspecific immune elements such as migration inhibition factor (MIF), which prevents the

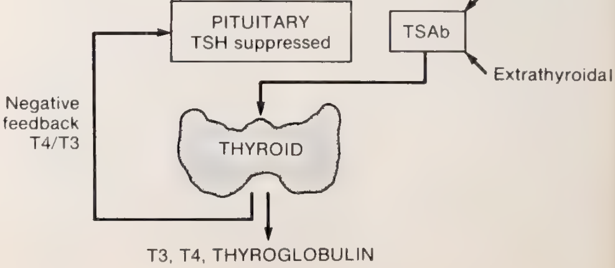

Fig. 6. Action of thyroid-stimulating antibodies (TSAb).

migration of cells away from the immune response. Thyroid antigens induce MIF activity in patients with Graves' and Hashimoto's disease. The addition of normal T cells to such MIF preparations inhibit the antigen induced effect suggesting that normal T cell preparations provide some factors which inhibit the sensitization response (91, 92). The mechanisms for these influences and their relationship to thyroid disease requires further unraveling.

Immunogenetics of Thyroid Disease

Both Graves' disease and autoimmune thyroiditis are familial diseases in the sense that both may occur, and indeed often do, within the same extended family. Thyroid disease is also found in families with other autoimmune diseases such as diabetes, pernicious anemia, Sjögren's syndrome, rheumatoid arthritis and Addison's disease (15). In keeping with this has been the increased frequency of HLA-DR3 and B8 in Graves' patients and the delineation of goitrous and nongoitrous autoimmune thyroiditis associated with HLA-DR3 and DR5 (41), respectively. However, these are imperfect genetic markers since over 40% of patients may not show such HLA-associations. The role of immunoregulatory genes and allotypic restriction in patients with autoimmune thyroid disease remains to be fully explored (42).

Thyroid Dysfunction in Pregnancy

Prevalence of Thyroid Dysfunction

Autoimmune thyroid disease is found in about 1–2% of the general population but has a marked preference for women in the reproductive age range where 5–15% may be affected (119). Studies on the prevalence of thyroid disease in pregnancy have been relatively few. It would appear that significant thyroid disease complicates about 0.5% of all pregnancies, approximately 0.2% hyperthyroid and 0.6% hypothyroid, much less than expected (Table 4) (90). Pregnant patients make up about 1% of patients with thyroid dysfunction (98). In addition, between 5 and 9% of women have detectable thyroid dysfunction in the postpartum period, much of which appears to be transient in nature (see under "Nature and Prevalence").

TABLE 4
Prevalence of Thyroid Dysfunction in Pregnancy and Postpartum Period

	Prevalence (%)		
Status	Nonpregnant (119)	Pregnant (90)	Postpartum (11)
Hyperthyroid	1.9	0.2	—
Hypothyroid	1.4	0.6	—
Painless transient dysfunction	—	—	7.0

Fertility and Thyroid Disease

Prevalence studies indicate a marked reduction in fertility associated with thyroid dysfunction. On a clinical basis this is reflected in menstrual irregularity and anovulation in both hyper- and hypothyroidism (17, 54, 106, 117) and a marked rebound in fertility during the early stages of treatment of the disorder. It is therefore, imperative that patients be warned of the increased risk of pregnancy at the initiation of treatment. Hypothyroid females have ovulatory failure, inadequate corpus luteum formation, and menorrhagia in up to 70% of cases. Hyperthyroid women have oligomenorrhea or scanty menstrual flow in up to 90% of cases and half such patients fail to ovulate. The physiological mechanisms for these disturbances in normal ovarian function appears to lie at a number of levels:

1. The hyperthyroid pituitary demonstrates exaggerated responses to gonadotropin-releasing hormone (GnRH) which presumably interupts the finely tuned control of gonadotropin spikes that dominate the ovulatory sequence (Fig. 7) (3, 5, 28).
2. Levels of sex hormone binding globulin (SHBG) are elevated in hyperthyroidism and estrogens, both bound and free, are also increased in both sexes. This results from both an increased production rate, via excessive conversion to testosterone to estradiol and androstenedione to estrone, together with decreased clearance, perhaps related to increased SHBG levels (4, 99, 113). The opposite occurs in thyroid failure although SHBG levels may remain unchanged.
3. The ovary is also known to accumulate iodine and to be dependent on thyroid hormone for normal function (20, 101, 102).

The impact of thyroid hormone deficiency or excess on the reproductive process is therefore complex (Fig. 8) and many areas of normal physiology may be interupted. We have no reliable data on the influence of thyroid hormone status on female sexuality although it is well known to affect male potency and fertility (37, 67).

Who Should Treat Thyroid Disease in Pregnancy?

Pregnancy is the ultimate endocrine function test. The understanding of the reproductive pro-

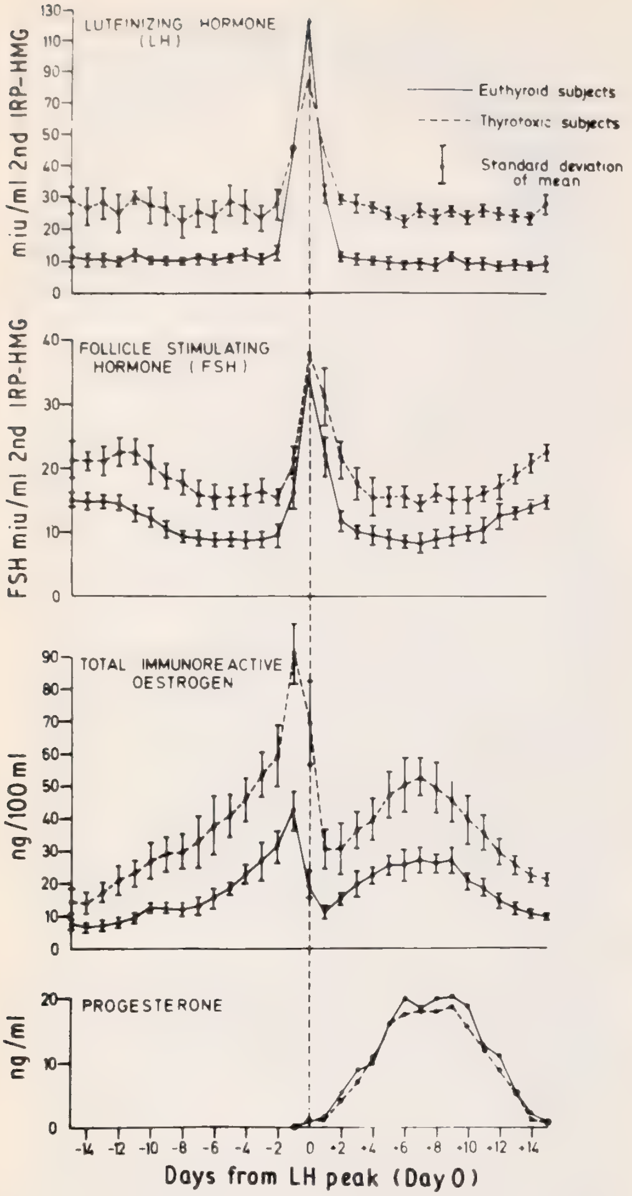

Fig. 7. Gonadotropin levels in hyperthyroid women through the menstrual cycle. Graphs were constructed around day of LH peak (Day 0). From E. O. Akande and T. D. R. Hockaday: Br J Obstet Gynaecol, 82:541–551, 1975 (5).

cess requires a high degree of expertise, far beyond the ability of most endocrinologists. However, the thyroid gland is not only an unbelievably complex organ, but its diseases appear to be unique and highly complex. The high prevalence of thyroid disease in the population means that many physicians have intimate knowledge of thyroid diseases and their vagaries. We believe, therefore, that is is common sense, supported by mortality and morbidity changes, that thyroid disease in pregnancy requires dual care by both obstetrician and endocrinologist, working as a team with the common goal of caring for both mother and fetus in the short and long term. This approach allows a few interested individuals to share their expertise for the general good of the community.

Hyperthyroid Graves' Disease in Pregnancy

Presentation and Diagnosis

The syndrome of Graves' disease has three separate facets: thyroid dysfunction, ophthalmic involvement, and the dermatological manifestation usually referred to as pretibial myxedema. Systemic symptoms such as fatigue, heat intolerance, emotional lability, and hyperhidrosis are often part of normal pregnancy accompanied by tachycardia and hyperdynamic systolic murmurs. Such symptoms can never be a reliable guide to hyperthyroidism. Failure to gain weight adequately may be one of the more helpful clinical signs. The size of the thyroid in pregnancy may increase (see under "Thyroid Function Testing"), but a visible goiter is likely to be an indication of thyroid dysfunction in most patients. The classical signs of Graves' disease such as ophthalmic and skin changes make the diangosis straightforward (Table 5). However, in all patients, biochemical parameters with reference to the normal pregnant ranges have to be carefully evaluated before a therapeutic decision can be made.

Morbidity and Mortality

Since many patients with severe thyrotoxicosis are amenorrheic or anovulatory, fertility is impaired, and often hyperthyroidism is observed in the setting of a partially treated female who has been on antithyroid drugs and subsequently becomes pregnant. Careful management with consideration to physiologic principles is essential for the avoidance of maternal and fetal morbidity and mortality. Maternal complications of untreated hyperthyroidism now occur rarely but may still be life threatening in the severe case with accelerating hyperthyroidism and conges-

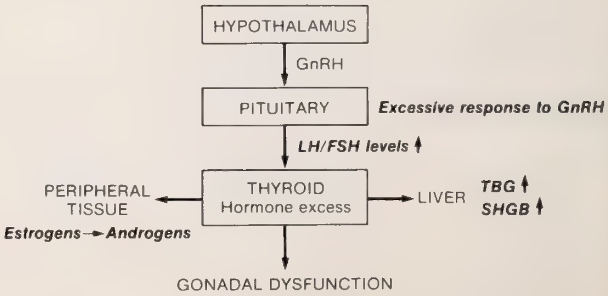

Fig. 8. Mechanisms of thyroid hormone influence on reproduction.

TABLE 5
Diagnostic Signs in Graves' Disease

System	Sign
Eyes	Periorbital edema Conjunctual injection Exophthalmos Muscle dysfunction
Skin	Pretibial myxedema
Thyroid	Visible, soft, diffusely enlarged gland

tive heart failure resulting in maternal death. It has been estimated that in untreated hyperthyroidism early fetal loss may be as much as four times greater (6.6 vs. 1.6%) if the mother is untreated (51, 79). Prematurity and congenital anomalies are not increased above the level of the general population and the increased fetal loss has been associated with a higher stillbirth rate (see under "Neonatal Period and Prediction of Neonatal Graves' Disease").

Treatment of Hyperthyroidism

General Approach. An antithyroid drug regimen is the appropriate treatment for most cases of hyperthyroidism in pregnancy. Radioactive iodine is contraindicated. In the past, surgery during the midtrimester of pregnancy after preparation with antithyroid drugs was considered advisable (63). Subsequently, however, many series have been published with favorable results from the use of antithyroid drugs alone thus avoiding the risks of anesthesia and surgery (14, 55, 87, 129). This is our standard therapy for hyperthyroidism in pregnancy at The Mount Sinai Hospital. Surgical intervention is reserved for those patients with significant drug intolerance.

Our aim in the therapy of pregnant hyperthyroid patients is to reduce the circulating free T_4 concentration into the high normal or just elevated range. We believe that earlier poor results from medically treated patients were a direct consequence of difficulty in measuring the free hormone indices or failure to perform frequent thyroid function monitoring. A free hormone index (e.g. T_4:TBG,FTI) must be measured frequently in order to prevent falling levels and avoid excessive fetal thyroid blockade by antithyroid drugs. TSH monitoring is additionally useful and highly recommended. Often the drug dosage requires relatively rapid tapering since we prefer to act when the T_4 is falling rather than waiting until below normal levels are achieved and TSH is increasing. Once the TSH is elevated the fetus must have been exposed to excessive antithyroid drug.

Antithyroid Drugs. When the diagnosis of hyperthyroidism has been established by appropriate thyroid function tests, including antibody titers, antithyroid drugs can be introduced. Propylthiouracil (PTU) and methimazole are thionamide drugs which act by blocking thyroid hormone synthesis at the stage of organification and iodotyrosine coupling (Fig. 2). Inhibition of peripheral deiodination by PTU has been much discussed but appears to be unimportant at normal therapeutic doses. Because of the rare occurrence of fetal aplasia cutis reported with methimazole (87), PTU has been our standard antithyroid drug for use during pregnancy. There appears, however, to be no other advantage over methimazole.

Therapy should begin with as low a dose as possible, e.g. 50 mg PTU q.i.d., a dose lower than normally prescribed in nonpregnant patients. Since the drug interrupts organifications, its action is not reflected in circulating hormone reduction for 7–10 days depending on the level of preformed hormone left in storage within the gland, and in many patients a therapeutic effect may not be seen for 3 or 4 weeks. As the free T_4 index falls the dosage is reduced as rapidly as possible. The aim is to be prescribing no more than 50 mg in the last months of pregnancy.

The commonly used block and replacement regimen is not appropriate in pregnancy. Because of the unpredictable and generally poor transplacental passage of thyroid hormone, supplementation with either T_4 or T_3 provides a false sence of security, making the mother euthyroid while continuing fetal exposure to higher doses of antithyroid drugs than would be necessary without thyroid hormone supplementation.

Adjunctive therapy with stable iodine is rarely justified, as it crosses the placenta easily and may be responsible for large goiters leading to dystocia, fetal hypothyroidism and fetal death (50). Propranolol, a β-adrenergic blocking drug used to control the sympathomimetic symptoms of hyperthyroidism in nonpregnant patients, has been associated with placental insufficiency, intrauterine growth retardation, excessive uterine irritability, and fetal bradycardia (97). However, reports of fetal hypoglycemia, hyperbilirubinemia, and polycythemia have not been substantiated. There has been recent controversy regarding the use of propranolol in hypertensive pregnant patients (24, 59, 74, 105) and its occasional uneventful use in hyperthyroid pregnancies has been reported (70). At present we recommned propranolol during pregnancy only in more severe thyrotoxicosis or preoperatively when antithyroid drugs are contraindicated and, where used, discontinued 24–48 hr prior to delivery if possible.

Fetal Impact of Antithyroid Drugs. Previous studies have emphasized the need for the smallest dose of antithyroid drug. Even with low doses of PTU (100–200 mg daily) the mean cord serum T_4 may be lower than in controls (27, 69). An exaggerated TSH response on day 1 may be a reflection of such mild hypothyroidism (27). In one such study 7 of 11 mothers had received either T_4 or T_3 supplements (27). Thus, assurance of maternal euthyroidism does not guarantee freedom from neonatal hypothyroidism. We, therefore, taper antithyroid drugs rapidly and find that minimal doses in the range of 50–100 mg of PTU or less is all that is necessary to achieve euthyroidism in the third trimester. Attempts at providing the fetus with thyroid hormone by the use of intra-amniotic or placental delivery and placental-passing analogs have also been reported.

The clinical relevance of excessive transient neonatal TSH elevations, described above, is uncertain since subsequent growth and development of such children is known to be normal (22, 81). Using a regimen of antithyroid drug therapy similar to ours, recent studies have indicated no fetal goiters and no obvious hypothyroidism (69).

Subtotal Thyroidectomy in a Pregnant Patient. In the case of a pregnant hyperthyroid patient who sustains major drug toxicity (marked leukopenia, significant liver disease), surgery may be the only means of successfully effecting euthyroidism. Subtotal thyroidectomy in the nonpregnant patient results in a cure rate of over 80%, with hypothyroidism occurring in about 15% and recurrent disease in approximately 5% depending upon the experience of the surgical teams involved. Recurrent laryngeal nerve injury and permanent hypoparathyroidism are unusual with a subtotal procedure but remain a significant risk outside major centers (43, 46, 76, 118).

Anesthetic complications in pregnancy are apparently no greater than in the general population and fetal losses are not increased in euthyroid patients. However, untreated pregnant thyrotoxic patients in their second trimester have been reported to have increased rates of abortion, intrauterine death, and stillbirth rates affecting 10–25% of cases (63). The use of propranolol before, during, and following such surgical intervention has helped greatly in the management of these patients, and for the brief exposure time to which the fetus is subjected to the drug is perfectly justifiable (72). Complication rates with such treatment have not been reported for a large enough series to remark on its precise impact on outcome.

Management of Labor in Graves' Disease. Most pregnant hyperthyroid women will have been reasonably well controlled with antithyroid drugs by the time labor ensues. A euthyroid patient seems to sustain no increased risk of complications of labor or of exacerbated hyperthyroidism. In the case of a patient who has previously escaped medical therapy and arrives at the hospital in labor or close to term with untreated hyperthyroidism, more drastic measures are necessary to avoid the risk of severe accelerated hyperthyroidism precipitated by the stress of labor and delivery. The poorly prepared patient should be started on blocking doses of antithyroid drugs at the start of labor and begin intravenous sodium iodide therapy to block the release of preformed thyroid hormone from the thyroid gland. The β-blockers such as propranolol may be used cautiously in the event of tachycardia and circulatory distress. Oral or parenteral corticosteroids (e.g. dexamethasone 2 mg q.i.d. for 24 hr) should be added since there is evidence that they rapidly decrease circulating T_3 levels (128) and may reduce the morbidity of what is often termed "thyroid storm." Steroids may affect thyroid hormones by decreasing thyroid cell prostaglandin action at the level of the thyroid and reducing hormone release. In addition they may inhibit peripheral deiodination to T_3. This combination drug regimen reduces maternal morbidity without undue danger to the fetus. However, complications in the presence of such an accelerating degree of hyperthyroidism remain significant. Thankfully such acceleration has been known to be unusual in the pregnant thyrotoxic for many years (51) and separate mortality and morbidity figures are not available.

Neonatal Period and Prediction of Neonatal Graves' Disease. Major and Munro (77) first suggested in 1960 that neonatal hyperthyroidism may be caused by transplacental passage of TSAb. We now know that neonatal thyrotoxicosis occurring as a result of transplacental thyrotoxicosis occurring as a result of transplacental passage of TSAb is rare, occurring in less than 1% of mothers with Graves' disease (82, 88). It may also be seen in babies whose mothers are euthyroid on T_4 during pregnancy following previous thyroid destruction for Graves' disease but have persistent high TSAb levels. Because of the placental passage of antithyroid drugs neonates who have been exposed to high titers of TSAb may not demonstrate symptoms of neonatal thyrotoxicosis until they have been discharged from the nursery. This is because the half-life of antithyroid drug action is approximately 10 days while that for the action of TSAb may be over 3 weeks. Maternal TSH blocking antibodies with a shorter effective half-life than TSAb have also been suggested to be a cause of delayed neonatal hyperthyroidism in mothers who have conincidental TSAb but this has to be distinguished from thyroid desensitization (133). Much depends on the maternal antithyroid drug regimen in the last weeks of pregnancy. Babies of mothers with high titers of TSAb and no antithyroid drugs may, however, have obvious neonatal hyperthyroidism soon after birth.

Neonatal Graves' disease persists for as long as the TSAb is present at a sufficient concentration in the circulation. The disease is therefore transient and must be distinguished from the early onset of Graves' disease in the infant or young child. This latter situation is unusual in early childhood and may be recognized by persistent, or newly developed TSAb levels.

The physician caring for an infant at risk must be alerted to check for tachycardia, fever, congestive heart failure, failure to gain weight and failure to thrive in the first weeks of life, rather than awaiting the customary one month "well baby" examination. The use of TSAb and/or TBI assays in the prediction of neonatal hyperthyroidism has received considerable attention and has found its place in routine clinical care in a number of centers (88). It has been felt that the transplacental passage of TSAb is responsible for the development of the neonatal thyrotoxicosis and recent studies have indicated that only those patients with markedly elevated titers during pregnancy deliver babies who are at risk for the development of neonatal thyrotoxicosis. It is to be hoped that in the near future quantitative assay of TSAb will be available to all pregnant patients with a history of autoimmune thyroid disease as a means of predicting which infants will be at greatest risk. A mother may have had a subtotal thyroidectomy or radioiodine ablatin for Graves' disease and be maintained on thyroxine replacement. Such patients may have persistent TSAb in high titer and treatment with antithyroid drugs may be initiated in order to treat the fetus itself. Careful monitoring of the fetus for hypothyroidism under such conditions is more than difficult and probably would require intra-amniotic monitoring of thyroid function.

Ophthalmic Graves' Disease. The retro-orbital accumulation of inflammatory cells leading to swelling and destruction of orbital muscles and hypertrophy of adipose tissues is considered to be an autoimmune disease of uncertain etiology (for review, see Wall et al (124)). There are no known specific antibodies and the disease course does not parallel the thyroid dysfunction. It may even be seen without any detectable thyroid involvement, so-called euthyroid ophthalmic Graves' disease. Treatment of the hyperthyroidism does not usually influence the ophthalmic abnormality unless hypothyroidism ensues causing the retro-orbital swelling to become even worse. The disease can be considered as a separate, closely linked, inherited abnormality with the genes for Graves' thyroid and ophthalmic disease occurring close together. Eye disease is clinically apparent in about 15% of cases of Graves' disease and we have never seen an excerbation during pregnancy.

Autoimmune Thyroiditis and Hypothyroidism in Pregnancy

Presentation and Diagnosis

Because significant thyroidal insufficiency may be associated with ovalatory failure (see Under "Fertility and Thyroid Disease") such patients usually are known to have thyroid disease and may have discontinued their medication. In addition, previous thyroid surgery and radioactive iodine treatment must be excluded. The clinical presentation in such cases remains typical of the nonpregnant woman with marked lack of energy, excessive weight gain, general malaise, cold intolerance, dry skin, constipation, myalgia and early fatigue. Hence, there is often a marked contrast to the usual hyperkinetic state of a normal pregnancy. Typically, however, the pregnancy is progressing normally despite the maternal thyroid failure.

Diagnosis is confirmed by the measurement of T_4 and a binding assessment, TBG or T_3 resin uptake, and a raised TSH. Autoimmune thyroiditis is indicated by significant thyroglobulin and microsomal antibody titers and perhaps by a family history of autoimmune endocrine disease. Any significant increase in TSH (more than 10 μU/ml) during pregnancy indicates thyroid insufficiency and requires therapy.

Morbidity and Mortality

In untreated patients the rate of first trimester fetal loss may approach 50% (62) with a 20% rate of stillbirths and neonatal deaths (57). Recent studies suggest, however, that good obstetric practice is as important as treating the hypothyroid mother with replacement therapy (85). However, there have been no larger studies of untreated patients in recent years and let us hope that none is performed. With mild elevations of TSH the fetus is at little risk since it does not cross the placenta and fetal thyroid function will be normal. Hence occasional lapses in therapy are of little consequence to the baby.

Treatment of Hypothyroidism

The New Patient. Appropriate therapy is replacement with thyroxine itself, adequate to bring the maternal calculated free T_4 index into the normal pregnant range with concomitant suppression of TSH. T_3 is provided via peripheral deiodination of administered T_4. There is no evidence to suggest that additional T_3 therapy is necessary. Elevations in TSH, indicating inadequate replacement, probably have no effect on the fetus since TSH does not cross the placenta (85). During a normal pregnancy the metabolic clearance rate of T_4 does not change so that the dose of T_4 required to achieve euthyroidism does not differ from the normal nonpregnant woman and most importantly, from the same patient prior to pregnancy (48).

The use of thyroid extract is no longer acceptable and such preparations have already been withdrawn from some European markets. Their problem is one of unpredictability in the preparation and, in particular, the high serum T_3 levels which patients may develop.

Treated Hypothyroidism. Since the MCR for T_4 remains unchanged during pregnancy most patients who are already on long-term replacement therapy will not need their dosage adjusted. Nevertheless it is important to monitor T_4 and TSH during the pregnancy. Occasionally such patients will require increased T_4 but in our experience this is unusual. It may be secondary to poor compliance for a variety of reasons including the fear of harming the baby by taking a drug. Careful explanation to all patients on T_4 will help avoid such problems.

Fetal Impact of Maternal Thyroid Antibodies

There appears to be no fetal impact by placental passage of maternal thyroglobulin and microsomal antibodies (94). Presumably an abnormal immune system, including appropriate killer cells, is necessary for thyroidal destruction. Alternatively, the fetal thyroid may be particularly resistant to destruction. We have to remember that titers of such antibodies in the maternal serum are depressed by the end of pregnancy and passage of suppressive cells to the fetus may also be protective (125).

One antibody in women with autoimmune thyroiditis has been reported to be associated with neonatal hypothyroidism, the TSH receptor blocking antibody discussed under "Thyroid Stimulating and TSH Receptor Antibodies." Familial neonatal hypothyroidism associated with maternal and fetal antibodies to the TSH receptor which do not stimulate but block TSH action may be more common than presently envisaged (40, 80). Nevertheless, if real TSH receptor blockade was occurring throughout pregnancy, the fetus would have a reduced thyroid hormone supply for its development. The developmental outcome in such cases is uncertain. Clearly TBI screening will provide more information on this perplexing situation.

The Postpartum Thyroid Syndromes

Nature and Prevalence

The onset of autoimmune thyroid disease in the postpartum period has been known since the earliest description of the disease (95). Pregnancy induces dramatic suppression of both humoral and cell mediated immunity (see under "Immune Function"). In the postpartum state, reversal of this phenomenon may induce rebound activation of autoimmune disease, with marked increases in thyroid antibody titers (Fig. 9). Roberton (100) in 1948 recognized the increased frequency of postpartum thyroid failure in patients with goiter and it was Amino (7) in 1976 who reawakened interest in the autoimmune nature of the postpartum syndromes. During the last decade, postpartum thyroiditis has been recognized with increasing frequency, with an incidence of 5.5% in Japan (11) and up to 8.9% in the United States (120a). The varied presentation and course of the disorders indicates that multiple factors are responsible for the thyroid dysfunction (Fig. 10).

Transient Postpartum Thyroiditis

Patients who develop thyroiditis in the postpartum period may present in either a hyper- or hypothyroid phase, the former usually preceding the latter (6). A painless thyroid enlargement is common but occasionally tenderness may occur. Patients may have history of previous autoim-

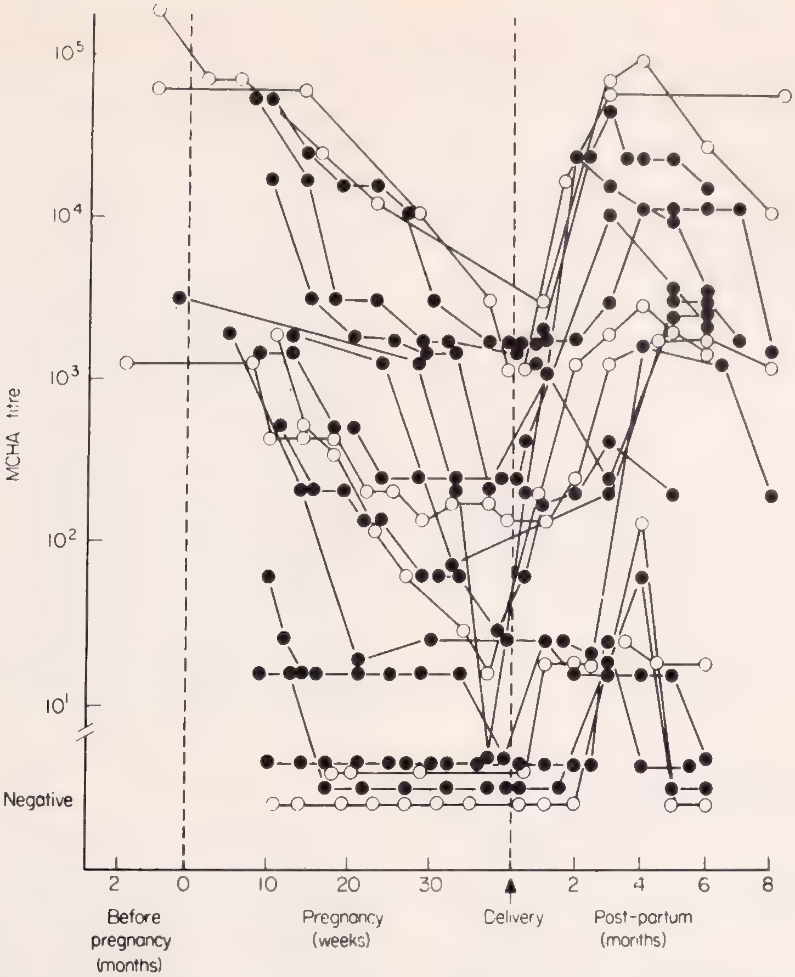

Fig. 9. Changes in thyroid microsomal (MCHA) antibodies during and after pregnancy in patients with Graves disease (○) and autoimmune thyroditis (●). From N. Amino et al.: Clinical and Experimental Immunology, 31:30–37, 1978 (9).

mune thyroid disease but typically this is not the case and thyroiditis is not expected.

Patients seen in the hyperthyroid phase of thyroiditis have "destruction induced" hyperthyroidism similar to that seen in subacute thyroiditis and occasionally seen at the onset of a more classical Hashimoto's thyroiditis (52). Radioiodine uptake is low, sedimentation rate may be normal or only mildly raised, the T_3:T_4 ratio may be low due to excessive T_4 release, and thyroid aspiration biopsy reveals lymphocytic infiltration. The disease is generally brief in duration, occurring 2–4 months postpartum, and is more than often followed by a transient hypothyroid phase as described below. Titers of thyroid antibody, in particular, microsomal antibody, are characteristically high (9). Hyperthyroid symptoms may be treated with β blockade in most cases and a return to euthyroidism or development of thyroid failure monitored. Antithyroid drugs are best avoided since they are unlikely to be helpful in a thyroid undergoing inflammatory destruction, cloud the onset of thyroid failure, and in addition, introduce complications for mothers who are breast feeding (see under "Breast Feeding and Thyroid Disease").

Patients who present initially with transient hypothyroidism may have had a preexistent hyperthyroid phase with glandular destruction which was not diagnosed. Recovery to the euthyroid state may take 3–5 months. Diagnosis is made on the bases of thyroid function tests, particularly a raised TSH level, high antibody titers, and lymphocytic infiltration on biopsy (45). Treatment with thyroxine is often required to alleviate symptoms of fatigue and weight gain, and may need to be continued for a period of 6 months. Attempts should then be made to withdraw therapy and determine if the disease is permanent or transient.

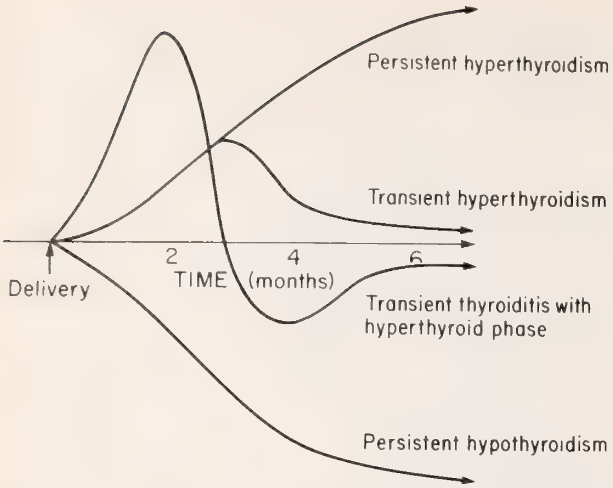

Fig. 10. Representation of natural history of postpartum thyroid syndromes. Adapted from N. Amino and K. Miyai, in T. F. Davies (ed.): Autoimmune Endocrine Disease. Wiley, New York, 1983 (6).

Transient "Stimulator-Induced" Hyperthyroidism

Some patients present with thyroid enlargement and hyperthyroid function tests but with increased rather than decreased radioiodine uptake. This syndrome may have a slightly later onset than classical thyroiditis and persist for 4–6 months (6). Our interpretation of this disorder has been that it represents a transient form of Graves' disease but the failure to demonstrate TSAb in such cases leaves this as speculation (12). However, the difficulty in demonstrating TSAb with some assay methods leaves such data requiring confirmation.

Permanent Thyroid Disease

Both Graves' and Hashimoto's disease are known to present for the first time in the postpartum period. This was often assumed to be just coincidence but our understanding of the immune changes in the postpartum period indicates that such patients decompensate for understandable reasons. Often such patients have had a previous history, usually Graves' patients, and recurrence is diagnosed in the postpartum period (8, 39). Treatment of these conditions is the same as for the nonpregnant patient with particular attention to breast feeding taking place.

It is also important to note that we are at present uncertain of the long-term natural history of transient postpartum thyroid disease. Many such patients may proceed to chronic thyroid dysfunction within a few years of pregnancy. The epidemiology of such disorders requires further exploration.

Why Do Patients Often Recover From Postpartum Thyroid Disease?

The ability of patients with marked thyroiditis and high thyroid antibody titers in the postpartum period to ultimately regain control of their immune system and suppress autoantibody secretion is one of the great enigmas of thyroid immunology. Such individuals obviously have the inherited clones of thyroid antibody secreting cells which, during a particular interlude, are allowed to expand and cause thyroid cell destruction or stimulation. The factors which allow such expansion and their ultimate suppression most likely lie in the families of specific helper and suppressor T cells which ultimately control B cell differentiation (9). Understanding this sequence of events may allow us to help patients with chronic thyroid disease regain control of their autoantibody secreting repertoire.

Breast Feeding and Thyroid Disease

Most women with thyroid dysfunction come successfully to term and deliver normal infants. Many are concerned about the risks and benefits of nursing in this special situation. T_4 is present in breast milk and may be beneficial to the congenitally hypothyroid baby (19). No evidence has linked postpartum hyperthyroidism with excessive thyroxine passage via breast feeding, indeed the mothers' metabolic status appears to be irrelevant to the infant. Antithyroid drugs, however, enter breast milk and most physicians have persuaded mothers not to breast feed under such circumstances. Early data suggested that the concentration of antithyroid drugs in breast milk may be significant enough to influence the child's thyroid function (75). More recent data with improved analytical techniques have suggested that drug levels are much lower than originally thought (68, 116). Hence antithyroid drugs are not an absolute contraindication to breast feeding assuming the mother is taking a low dose and that infant thyroid hormone levels can be monitored. We continue, however, not to recommend breast feeding if antithyroid drugs are essential.

Little is known of the consequences of thyroid antibody transfer to the neonate via breast milk and high titers are not a contraindication. Obviously the nursing mother must not be given radioiodine either for diagnostic purposes or treatment in the postpartum period since iodine is also secreted by the breast.

Other Thyroid Diseases in Pregnancy

Multinodular Goiter

The cause of multiple nodule formation throughout much of the thyroid gland is unknown. Theories include hypersensitive TSH receptors in clones of thyroid cells and innate hyperactivity of the follicular cell at the post receptor level (33). The follicular heterogeneity of the normal thyroid has been recently well documented (96) indicating the potential for nodule development in all thyroid tissue. If a patient has previously been on thyroid hormone suppression therapy with the hope, often unfulfilled, of suppressing futher enlargement, then this should be continued throughout the pregancy without change. Withdrawal may reveal permanent hypothyroidism due to an associated autoimmune thyroiditis and is not recommended during pregnancy. In the euthyroid patient, observation is all that is required.

The Thyroid Nodule

About 5% of the population have one or more palpable nodules in the thyroid and this rate increases with age (36). The development of a single thyroid nodule during pregnancy is unusual but the great concern is the possibility of a rare thyroid carcinoma. Thyroid biopsy is the investigation of choice along with routine thyroid function tests (107). Thyroid scanning is contraindicated but this is one time when ultrasonography may be very helpful. A diagnosis of definite or suspicious malignancy should lead directly to surgical therapy. When the biopsy is benign and the nodule is enlarging, then an attempt at thyroid hormone suppression can be introduced without any risk to the fetus.

Subacute Thyroiditis

Subacute thyroiditis is considered to be a viral-like inflammation of the thyroid gland which may present with a painful or painless enlargement associated initially with release of thyroid hormone from damaged tissue followed by thyroid failure when widespread cell death occurs (36). It may be associated with the transient appearance of thyroid antibodies in low titers in susceptible individuals (122) and increased T suppressor cells (123). Most patients then have total recovery of normal thyroid function. The onset of painful subacute thyroiditis in pregnancy is rare. The present authors have never seen such a case. Should it become apparent then thyroid hormone supplementation may be needed for the hypothyroid phase. Low dose steroids for extreme pain are contraindicated and are not recommended because of their influence on the fetus. The painless variety has to be distinguished from autoimmune thyroiditis (Hashimoto's disease) by the absence of thyroid antibodies or their transient presence in low titer (64). Similarly, in the postpartum period the two syndromes may be distinguised by thyroid antibody titers since both will exhibit low radioiodine uptakes.

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VOLUME 52 NUMBER 2 FEBRUARY 1985

CONTENTS

THE COMPUTER IN CLINICAL DECISION MAKING

Introduction *Carl F. W. Wolf, M.D.* 79

Some Preliminary Remarks *Eric Brodheim Sc.D.* 80

Information Management Systems in Neonatal Intensive Care: A Case Report *William W. Frayer, M.D.* 82

Artificial Intelligence Methods for Expert Medical Consultant Systems *Casimir A. Kulikowski, Ph.D.* 87

The Computer as a New Basis for Analytic Clinical Practice: Coupling Individual Problems with Medical Knowledge *Lawrence L. Weed, M.D.* 94

GENERAL ARTICLES

Cesarean Section Patterns: Influence of a Perinatology Service *Norbert Gleicher, M.D., Michael Vermesh, M.D., Ziggy Rotmensch, M.D., John Thornton, Ph.D., and Haim Elrad, M.D.* 100

Optimal Delivery of Nonvertex Twins *Bernardo Ismajovich, M.D., Edmond Confino, M.D., Anat Sherzer, M.D., Arie L. Lidor, M.D., and Menachem P. David, M.D.* 106

Contents continued inside

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Volume 52
Number 2
February 1985

CONTENTS *continued*

Amniotic Fluid Microviscosity Analysis in Diabetic Pregnancies: Comparison with Other Methods of Lung Maturity Assessment Using Predictive Value Analyses *Naomi D. Neufeld, M.D., Lucille Corbo, B.S., Glenn D. Braunstein, M.D., and Joan Rasor, M.S.* 110

Electrocardiographic Patterns of Normally Functioning Dual Chamber Pacemakers *Alfonso O. Tolentino, M.D., Roger P. Javier, M.D., and Philip Samet, M.D.* 116

Factors Predisposing to Intraoperative Myocardial Infarction During Coronary Artery Bypass Surgery *Richard R. Schneider, M.D., Augusto D. Pichard, M.D., and Bruce Mindich, M.D.* 123

SPECIALTY NOTES

OPHTHALMOLOGY *Keith M. Zinn, M.D., Editor*

Postcryotherapy Dellen Formation in Diabetics with Proliferative Retinopathy *Michael Newton, M.D., and Keith M. Zinn, M.D.* 130

RADIOLOGY *Jack G. Rabinowitz, M.D., Editor*

Case 1 *Shelley K. Charnoff, M.D.* 133

Case 2 *Jerrold T. Gale, M.D., and Daniel Schlusselberg, M.D.* 136

SURGICAL PATHOLOGY *Ira S. Schwartz, M.D., Editor*

Solitary Cecal Ulcer due to Cytomegalovirus in a Leukemic Patient *Elise M. Rosen-Levin, M.D., and Ira S. Schwartz, M.D.* 139

STUDENTS' CORNER

Postoperative Pain Control: Review of Methods *Scott A. Berger, M.D.* 142

Protein-Calorie Malnutrition, Immunological Function, and Total Parenteral Nutrition in the Surgical Patient *Bryan G. Forley, M.D.* 148

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The Computer in Clinical Decision Making

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The Computer in Clinical Decision Making

Introduction

The papers which follow were presented at The New York Academy of Medicine in March 1982 as part of a symposium entitled "The Computer in Clinical Decision Making: What Roles and When?" which was sponsored by the Section on Biomedical Engineering of the Academy. When the program was arranged, the speakers were asked and graciously consented to represent three somewhat different approaches to exploitation of the computer in clinical decision making, ranging from the modest objective of "Better Data for Physicians in Their Traditional Role" to "The Computer with Artificial Intelligence as Expert Diagnostic Consultant" to perhaps the most ambitious topic, "The Computer as a New Basis for Practice by Analytic Clinicians of the Future."

Dr. Frayer's description of his information management system for a neonatal intensive care nursery emphasizes the importance of earning the cooperation of nurses and physicians in implementation. The reliable and timely capture of patient data by the providers of care then builds the foundation for a variety of more complex clinical computing applications. By efficient and comprehensive data collection and organization and the computation of useful derived functions normally calculated by the physician, the computer has facilitated the physician's traditional role without as yet drastically changing that role.

Dr. Kulikowski's review of the use of artificial intelligence methods to create expert medical consultant systems describes a discipline able to enhance interpretive reporting of laboratory tests or ultimately to mimic the analysis and learning which is characteristic of an expert physician consultant. How such systems will interact with individual practitioners and more traditional automated systems in the places where patients are cared for remains to be seen.

Dr. Weed's discussion of the computer as coordinator, record keeper, and medical knowledge resource is based on his experience with such an integrated system at the University of Vermont. His remarks are supplemented by a discussion of the problem of coupling existing medical knowledge, awesome in its vastness, with the problems of the unique individual patient each physician cares for. The latter paper was given as The Harold Lamport Memorial Lecture to conclude the symposium.

Clinical laboratory systems were not specifically covered in the program because they are already highly developed and in general use and their implementation and success is less dependent on, although far from independent of, the acceptance of practicing physicians and nurses. Numerous references, both recent and older, offer useful perspectives on that application of computers in clinical work. (For newer works, see Allen RD, Elevitch FR, eds. Computers in the clinical laboratory. Clin Lab Med 1983, 3. For older reports, see Krieg AF, Johnson TJ, McDonald C, Cotlove E. Clinical laboratory computerization. Baltimore: University Park Press, 1971.)

The contributors spoke from experience in both the development of concepts and the application of those concepts to real clinical problems. It seems clear that the larger challenge lies in achieving the application of computerized systems where patients are treated and physicians and nurses must accept them, use them, and be convinced of their benefits in daily practice. It is a truism that the future, with its possible perfection and myriad capabilities, must be built upon the present, with its imperfections and known frailties. These papers are intended to describe the present status of computer support for clinical decision making in the areas they address.

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Some Preliminary Remarks

"A decade ago few would have believed that there would be a hundred dollar machine that plays chess better than 90–95% of the population, or a set of programs that interprets electrocardiograms better than most doctors (and even better than some cardiologists)." This statement by S. Birnbaum (Computers: a survey of trends and limitations, Science 1982; 215 (4534): 764) highlights the recent acceleration in the pace of development of machines that process inputs in a manner that involves judgment based upon preprogrammed knowledge or knowledge acquired as a consequence of prior processing—something that is loosely called "artificial intelligence."

In the light of this rapid progress, how long will it be before artificial intelligence plays a role in medical practice? How will this come about? Will the medical information systems now coming into operational use provide increasingly better and more timely data to the physician continuing in the traditional role? Will these systems progressively expand not only to acquire and disseminate information, but also analyze it and act as an automated consultant? Will pilot projects that seek to organize knowledge in a manner to guide the medical decision making process bring about a restructuring of medical training and medical practice?

A recent symposium on this topic at The New York Academy of Medicine brought out that these are not "academic" questions, but developments that have advanced well into the pilot testing phase.

There are hospital wards with a computer screen at every bedside which will instantly record or retrieve information about the patient. The computer will furthermore perform many of the routine computations required for prescribing treatment, for instance computing dosage based on the stored patient weight and other pertinent data. With such a system, the ward nurse can maintain a central schedule for all pending transactions for patients in the ward and monitor to ensure that procedures are performed in a timely manner. The rough calculations that physicians must constantly make are performed automatically without possibility of mathematical error. These benefits are particularly significant in specialized wards such as those for premature babies, where there is an unusually high need for such calculations. With the decreasing cost of automated equipment, it is reasonable to presume that pilot projects now restricted to specialized wards will soon be economically feasible for every hospital bed.

The computer can do far more than store, retrieve, and perform calculations on data. It is changing the practice of medicine and having an impact on medical research. To cite just one example: computer-aided interpretation of electrocardiograms seems to be growing at a pace which, according to one study, suggests the "beginning of a period of rapid expansion of electrocardiographic processing by computers, resulting in substantial changes in the practice of electrocardiography." (Task Force III: Computers in diagnostic electrocardiography, Am J Cardiol 1978; 41:158–170.) This same study goes on to say that "computer analysis of electrocardiograms has had a substantial impact on basic research in electrocardiography, and has increased the feasibility of and capacity to carry out heart disease prevention programs and cardiovascular epidemiologic studies."

The computer can even be used to break medical decisions into a series of small steps called "frames" which guide clinical decision making step by step to improve thoroughness and logic. This Problem-Oriented Medical System (PROMIS) is an experimental development that reflects the vision of Dr. Weed, a vision he articulates in his article. It seeks restructuring of medical knowledge along problem-solving lines that are seen by some as a step toward establishing a highly detailed national standard for the practice of medicine (Fishman KD, The computer establishment, New York: Harper & Row, 1981). PROMIS was widely used at the University of Vermont with very encouraging, though highly controversial, results.

Medical practice will not be revolutionized overnight, whatever the power of computer technology and the achieved promise of pilot projects. There is a great deal of inertia, both for good and for bad, in medical practice and in the curricula by which the next generation of clinicians are trained. Artificial intelligence at its best can expand, supplement, and (to some limited extent) replace the human mind. This thought cannot fail but make any person, including the clinician, uncomfortable. There are grounds for this fear. A fairly unsophisticated approach to artificial intelligence resulted in a program called "Eliza" which was intended to mimic the behavior of a psychiatrist. To the shock of the researchers that developed it, sophisticated people who fully understood just what Eliza was and was not started pouring out their hearts to this collection of silicon chips. The implications go far beyond concern that unemployment may become a future factor in the ranks of psychiatrists. If such a simple program can provide such spectacular results during the infancy of artificial intelligence, where will it end? Will we be reduced by automata to unequal competitors for our daily lives? Such fears may be grossly exaggerated, but they have been raised by respected researchers and need to be taken seriously (see Weizenbaum J, Computer power and human reason, New York: W. H. Freeman, 1976). We are on the threshold of new horizons in clinical decision making, made possible by the computer and artificial intelligence. We must learn to use these tools not only imaginatively, but also humanely.

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Information Management Systems in Neonatal Intensive Care: A Case Report

William W. Frayer, M.D.

In virtually every area of our lives, both personal and professional, computer technology is becoming firmly established. For over twenty years, efforts to introduce computers in medicine have been reported. Computers have many responsibilities in banking, commerce, and industry which make them indispensable. Medicine has seemed a natural area for this technology, but despite the bright possibilities proliferation has not occurred, CAT scanning being the one notable exception. The single largest role for computers in medicine today is in the preparation of hospital bills and paychecks. Laboratory data systems are now beginning to be established more widely. But what about the bedside caretaker—does this age of technology offer anything to assist the physician in the traditional role of practitioner of the healing arts?

The availability of the digital computer as a tool for the clinician is unique among the many applications of technology in neonatal intensive care during the past decade. Unlike the precisely specified monitors and measuring devices which have proliferated, the successful performance of computer systems in clinical environments cannot be assured. Yet their enormous potential to facilitate both medical and administrative aspects of critical care medicine have led many hospitals to invest in the product and in its development. These investments have met with widely varying degrees of success.

One of the most searching of the many reviews of computers in medicine was by Friedman and Gustafson in 1977 (1). They reported an amazing mortality rate of over 80% for reported clinical systems, and concluded that many systems offered services for which there was little perceived need, and that the unneeded systems died of atrophy. If we wish to introduce, develop, and use computer systems in patient care, it is necessary first to establish a service for which there is a significant need and second to meet that need effectively. Once such a system is in place, it then becomes possible to explore a variety of exciting applications, which may be well or ill received without jeopardizing the existence of the data-processing system.

I would like to propose that the primary goal of establishing computerized information management as a tool for the clinician be defined as providing better access to data for the physician in practicing the traditional role of bedside caretaker. To illustrate how important this strategic view is, I describe in this report some of the experiences we have had at the Newborn Intensive Care Unit at The New York Hospital, New York City.

The Need. Neonatal intensive care is a specialty with an acute and worsening information management problem. For each patient between 600 and 1,000 new numerical values are typically generated daily. An organized presentation of this data is essential to the formulation of management plans. Locating the data, however, often proves more difficult than interpreting it. It is frequently dispersed—on the bedside flowsheet, in the chart, in interns' pockets, or still unreported by the laboratory. Frequently, more than one person needs access to the same document.

Although these problems create inconvenience they are generally not unmanageable in neonatal intensive care units with fewer than 25 beds. In larger units, however, traditional record-keeping systems are being overloaded. This overloading may lead to delayed recognition of significant clinical problems, and thus affect the quality of

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patient care. In addition, medical records may be less complete than they should be at a time when questions of liability demand improved documentation. It is not surprising that hospitals have begun to turn to computerized information systems to obtain the advantages of organized data retrieval and analysis that industry, commerce, and the financial community have enjoyed for the past twenty years.

Financial Viability. The application of computerized information systems in medicine is not a recent innovation. In most instances, high costs coupled with few cost-accountable benefits led to decreased support. It is now clear that clinicians who wish to use computers for routine patient care (without research grant support) must be prepared to assure both financial viability and user acceptance. Financial viability may be achieved in some applications on the basis of clinical service alone. For many applications, however, including neonatal intensive care, viability may be achieved by providing administrative as well as clinical data processing.

User Acceptance. User acceptance is a much more complex issue. Computers in medical environments encounter problems which are unique. In commercial or scientific applications, persons who either produce or use processed data rarely need to interact with the computer; specially trained people take care of this. In medical intensive care, the urgency of the situation is usually the reason for using a computer and precludes the delay imposed by employing intermediaries. If the computer system is to be successful, both doctors and nurses must interact directly with the system to enter and to retrieve data. Neither group has been trained to regard the computer as a natural tool of their profession. Consequently, if interaction with the computer is not both easy and beneficial, cooperation may be poor. Even when a computer system offers highly desirable retrieval features, if data are not reliably entered in a timely fashion, usability is reduced and acceptance will decline. User acceptance, then, is influenced by a series of characteristics including system response time, ease of data entry, and usefulness of retrieved data.

The approach to computerization has varied among intensive care units. In some settings computers have been introduced primarily to monitor or control specific processes, such as fluid infusion or cardiac arrhythmias. In such systems, information management may be a secondary consideration in both planning and evaluating performance. For neonatal intensive care, however, the nature of medical problems encountered as well as the physiologic limitations of the patient and the typically higher census in the unit establish information management as a high priority for computer system application. At present in neonatology, very few diagnostic or process control applications for computers have proven value. It is likely, however, that as computer systems become established in neonatal units such applications will develop.

Case Report

The neonatal intensive-care unit (NICU) at The New York Hospital-Cornell Medical Center is a 50-bed installation with 15 intensive care, 24 intermediate care, and 11 special care (convalescent) beds. It functions as a receiving center serving part of metropolitan New York City and a suburban area with approximately 20,000 births per year. During 1982, 1,200 infants were admitted for care.

In 1976, the medical center expanded its NICU from 25 to 50 beds in conjunction with a renovation of the facility. It was recognized that the data burden exceeded the capacity of the available staff. To facilitate patient care as well as administrative and clerical tasks, a computerized information system was installed. This was a logical starting point in terms of the operating needs of the unit. It also coincided with the view that the ability to store and recall data reliably is a cornerstone upon which clinical computing operations may be successfully built.

The original objectives of the NICU installation were to make accessible well-organized, up-to-date information on all NICU patients to anyone responsible for their care. This meant integrating bedside observations with monitored vital signs data and laboratory determinations into a centralized file. It was necessary to provide for convenient data entry for 50 patients and to make retrieval easy for caretakers. Laboratory data would be entered directly from the clinical lab which serves the ICU.

In planning the system, consideration was given particularly to the need for security or data safety in the event of a system malfunction, since it was not feasible to permit both manual and computerized record-keeping.

Because of the size of the ICU and the number of laboratory determinations, it was essential that the computer system be responsible for all charting of laboratory data reported through it.

All available commercial systems were considered at the time the NICU was being planned. It was decided not to attempt to create a system from components and original software. The reasons for this decision involved the complexity of the software needed and our lack of experience with this type of system, as well as the service problems arising when systems are supported by multiple vendors.

There was no commercially available computerized information system designed for ICU applications. However, the computerized monitoring system sold by Hewlett Packard offered several significant advantages. It was also a promising candidate for continued development as an information system, since it was programmed in FORTRAN and could readily accommodate additional application programs. The terminals were especially well suited for bedside use, with 16-key hand-held keyboards and video graphic capability. Virtually all system functions could be controlled easily from the bedside. All equipment in the system was covered by service contracts available from the manufacturer. The system seemed easy for users to operate.

The hospital purchased the system with several specified software modifications. These provided data entry capability using optical-mark reader cards, paged display sequences for retrieval which could be table-driven to link the displays to specific user-definable medical problems, and a report system for chart documentation. A programmer was hired from the outset to continue software development and to tailor the system for smoother operation.

The patient data management system we have installed has 30 data access points. Each ICU bed has its own keyboard and video display. In addition, there are 15 data access points located in other patients' rooms, staff rooms, at clerical and nursing work stations, in doctors' offices, and in the conference room. Two printers handle output destined either for the patients' charts or various administrative uses.

The central processor for the system was originally a 32K, 16-bit word minicomputer (Hewlett Packard 21MX-M). It has subsequently been expanded to 512K with a 50-megabyte disc. A second system with identical central processor and mass storage is operated for program development and is used for "spare parts" in the event of an equipment malfunction.

Data Collection. Data collection begins when a patient is admitted to the NICU and is assigned to a bed and identified for the computer system. A clerk enters preselected information concerning the patient, the family, referring physicians and hospital, as well as a brief medical history.

Throughout the hospital stay, all vital sign observations, intake/output and ventilation data observed at the bedside are entered into the system by the nurses caring for the patient. These values are printed out daily in the form of a flow sheet which is entered into the permanent record. Although data from bedside vital signs monitors are recorded and may be listed or plotted, these values are never entered into the chart record unless they have been verified by a human observer.

All bedside data entry was originally accomplished using optical-mark reader cards so that they could be re-read if data were lost or files damaged. Cards offered the advantage of being usable without access to a terminal and permitted the recording of computer readable data even when the system was not operational.

Laboratory data has been entered from the outset using a terminal located in the lab. Information is retrieved primarily at CRT terminals. There are several types of retrieval mechanisms; however, the most useful is accessed via a patient's medical-problem list. By selecting the problem for review, retrieval is initiated on all relevant data which are presented in a sequence of graphic or tabular displays. Initially, only raw data could be retrieved.

Problems. From the outset, we had the cooperation of both the medical and nursing staffs in the commitment to computerized record-keeping for the NICU. This was fortunate, since as we began to use the system, it became apparent that although it was technically capable of performing all of its specified functions, it was cumbersome to use, and response time, particularly during retrieval, was extremely poor. In some cases, it took over four minutes to retrieve data in response to a single keyboard command. Disc space limited the amount of patient data that could be stored at any time and there were frequent software problems which required that the system be restarted. Laboratory data has been very complete from the outset using terminal entry. However, the volume of this data is very small in comparison with the amount of bedside data which needed to be entered.

Although cards worked surprisingly well, entry errors occurred and frequently data were missing. It became common practice among nurses to delay the irksome task of filling out cards until the end of the shift. This delay of up to eight hours in data entry made the use of the system by other caretakers less helpful. In addition, if a systematic mistake had been made in card marking, it was possible to lose a whole eight-hour block of data when the person responsible for recording the data was not available for correction. It was clear that the system needed many changes. Our staff provided numerous suggestions which have served as the basis for the work we have subsequently done.

The use of terminals at the bedside for direct data entry offered many advantages if it were possible to enter both alphabetic and numeric information with a 16-key keyboard. It was also necessary to provide some insurance against data loss in the event of system malfunction.

Our initial approach to solving the first problem was to modify the keyboard data-entry program which had been in use in the laboratory to allow entering variables which are alphabetic rather than numerical. This has been implemented by permitting the user to select items from a multiple-choice list when alphabetic entries are required (for instance, infant formula, intravenous solution, urine dip-stick test results).

To provide data security, a tape transaction log was created which operates with a dedicated tape drive and logs all entries made at the time they are entered into the system file. If data are destroyed, the tape may be processed through the same entry program which handles keyboard entries, and the process of data restoration can occur with the system in full operation.

Despite these enhancements, however, we found that keyboard data entry was still unpopular in comparison with optical-mark reader cards. The reasons for this preference were delays in system response, along with the need for repetitive entries of data which remain the same from hour to hour (infant formula, caloric density, intravenous solution, dextrose content). Frequent monitoring of data flow sheets at that time indicated that the result of the system's level of performance, in addition to nursing dissatisfaction, was less complete patient records. With records incomplete, application programs written for physician users to analyze intake-output balances and caloric intake were essentially useless. It was common knowledge that these reports could not be relied upon.

The problems of system response time which seemed to be at the root of our difficulties were investigated further. However, it was concluded that patching of existing programs would not result in significant improvement. Consequently the approach to programming of this subsystem was substantially modified to reduce to a minimum the number of disc reads which were required in order to process a single data entry. New programming and system changes led to 3-fold to 10-fold increases in data entry speeds with a reduction in key strokes. In addition, provision was made to automatically copy forward all data types that are usually repetitive.

Successes. When this rewritten subsystem had been in operation for six months, card readers had been moved out of the unit and audits of patient flow sheets showed that patient data were more than 95% accurate and virtually complete; the lag for current observations was usually less than one hour.

Application programs which use this data are now being accessed more frequently by physicians. For example, one of the most useful computations was intake calories per kilogram per day—for many patients not perhaps an important number, but for premature babies one of the most important.

With the increased utilization of this program, which had been there for years but was only recently recognized, requests suddenly started coming in from our physician users for programs they thought would be helpful to them. This was a significant change and represented, in a sense, the coming of age of the project. We had been providing data at the bedside for a long time, but the question remained, Was it making any difference? Would the system be missed if it were gone?

In addition to medical users, administrative users started to request additional data processing. We now handle many medical and administrative reports that have to do with the referring hospital, reports to them and to their physicians, justifications of length of stay, billing information, and a variety of other statistics. This improvement in staff acceptance and participation came as evidence that the current phase of system development had earned full user acceptance and interest in assisting in further development.

Discussion

The application of computers to neonatal intensive care seems on first inspection similar to other ICU computer applications. In reality, however, the objectives and requirements are quite different. Monitoring, for most neonatal patients, plays a much less important role than for coronary-care or surgical intensive care patients. The purpose in turning to a computer was to draw together large amounts of observational and laboratory data.

Our experience since 1979 has shown us how challenging the seemingly simple task of storing and retrieving medical data in a clinical setting can be. At the outset, we were handicapped by lack of experience both within our unit and in the commercial marketplace. We have come to recognize that solutions to data management problems which seem ideal to "computer people" often are not acceptable to those who do not share this special interest. In other words, usability is ultimately determined by bedside users and not by programmers or system designers.

Perceived Reliability. As we have worked to modify our system to meet our users' needs, we rapidly became focused on basic issues such as data entry and system security. We have spent very little time on elaborate retrieval applications. Reliability has been an important consideration. Even with improved performance, attitudes were greatly influenced by the perception of reliability. Everyone always remembered the last system failure. The terminal being down constituted a failure for a bedside nurse. However, reliability has not turned out to be the most significant problem, since we now experience less than 24 hours of down time per year.

Availability of Data. Incompleteness was the problem which most determined whether users liked the system or didn't like the system. However, now that confidence in the availability of data is increasing, there is a growing list of programs we are being asked to write. User acceptance is increasing.

The Psychology of the User. Our basic view has been that information management for the purpose of facilitating direct care is a cornerstone which may be used for developing almost any type of clinical computing application. Achieving our present level of performance, however, has been a battle for inches. In retrospect, the original basic concept seems to have been sound. The system has had few conceptual changes. It looks the same as it did when it was first put in and seems from the outside to have been static.

For the people who have used it, however, things changed dramatically, and this is the most important thing. It required first-hand experience for us to be able to interpret the many human factors which have proven to be so important in achieving this level of acceptability. We've been aided by hardware updates, but technology has really not been the answer in determining success or failure. Our initial improvements came through what might be called psychological insights into our users; what factors motivated them, what made the system less approachable. Remember that computer operators do not run the system. If physicians want to know something, they have to touch the system, whether they like computers or not.

Tailoring to Fit. Why did it take five years for us to recognize things that seem so obvious in retrospect? We wrote only small programs in the beginning, but as we came to understand the system and the problem better, we became bolder in our modifications and consequently more capable of controlling those things which were ultimately going to effect the system's success or failure. Buying a computer is a lot like buying clothing: things seldom fit well off the rack. They also don't usually look too good if you make them yourself. Tailoring is required. Consequently, for us and many users across the country, the ability to tailor a system has turned out to be one of the single most important factors in determining success or failure.

Finances. From a financial viewpoint, our system has been cost-effective since installation, based on the laboratory charting functions which it performs (2). We continue to automate routine tasks whenever possible in order to improve the efficiency of our available clerical staff. In addition, computer-generated documentation is being used to improve insurance and governmental reimbursement for medical services.

Impact on Care. The impact of the data management system on patient care is difficult to assess. Patient stays are not shorter, and patient costs have increased over time. However, the computer has permitted us to modify our billing system to reduce bills by as much as 25% through improved charging accuracy. Although survival has improved, this improvement has occurred generally in NICU patients and cannot reliably be attributed to this particular technology alone. We are now caring for more patients without increased staff. It is now possible to provide better supervision of bedside care.

We have achieved our original objectives. We have laid the cornerstone for our system. Information management is that cornerstone, and the system can serve as the ideal proving ground for new ideas in medical data processng. The system's final form is as yet undetermined and its ultimate impact on neonatal intensive care has yet to be evaluated. Our experience suggests that bedside data management is both doable and affordable and offers tangible and intangible benefits as well as exciting opportunities for the future for physicians in their traditional role.

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Artificial Intelligence Methods for Expert Medical Consultant Systems

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One of the first questions commonly asked of researchers in artificial intelligence (AI) is, What do you mean by artificial intelligence? Although there are probably as many definitions as there are practitioners of this new discipline, a very general one has been given by Minsky (1): "Using the computer to perform tasks that are considered to require intelligence when performed by humans." In other words, without getting into a debate on whether the computer itself is intelligent, most researchers would agree that by very sophisticated programming methods we can produce programs that exhibit exceedingly intelligent behavior.

Reviewing the history of artificial intelligence, we see that the field spans a broad spectrum of activities.

At one extreme are researchers who are mostly interested in theories of human cognition, many of them being psychologists or computer scientists with a strong cognitive science background.

At the other extreme are those primarily interested in using the computer as an empirical tool for analyzing expert behavior, and producing working, high-performance systems. In the past few years some very accomplished systems which reproduce—or even improve on—the performance of expert medical specialists have been produced by researchers using AI knowledge-based, or expert systems, methods.

Knowledge-Based Systems: The Expert as Model. An expert system is a computer-based system that represents the expertise of a human specialist on the computer, has flexible strategies of reasoning, and can solve real problems the way a human specialist can. Typical problems handled by experts include advising on medical diagnosis, prognosis, or treatment; on geological exploration for oil or mineral deposits; on diagnosing and repairing high-technology equipment malfunctions; on analyzing and interpreting results from chemical or biochemical experiments; on interpreting laboratory instrument results; or on planning genetic engineering experiments.

The major idea behind expert systems is that they start out with a model of reasoning taken from the human expert. But they don't stop there, because we all know that human experts can be fallible. Experts may be very good at what they do but, like other humans, they sometimes make mistakes. To be considered experts they probably make mistakes less frequently, less obviously, and on less serious problems. If they are also more introspective and analytical in examining their own mistakes, they probably learn from their mistakes more quickly and do not repeat them.

We would also like an expert system to be capable of learning from experience, working from cases with well-established end-points, or solutions (stored in a data base). Nevertheless, the expert's model of reasoning is the starting point and cornerstone. The experts can come back and challenge one of these systems with new cases while the "knowledge engineer" builds it, but by no means are we saying that we're just looking at the reasoning of the expert and will settle for a direct simulation of it. We must carry out independent testing and incorporate the results of such learning experience in the "knowledge base" of our system.

Many of the projects in artificial intelligence in medicine have been linked through an NIH-sponsored computer network, AIM (2). Two large time-shared computers at Stanford and Rutgers universities provide a large part of the computing resources for the AIM community. My own research has been carried out at the Rutgers Research Resource on Computers in Biomedicine.

Starting in 1971, Dr. Sholom Weiss and I have

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developed many consultation systems. The first, developed in collaboration with the Mount Sinai School of Medicine, was CASNET—Causal Associational Network Model. It represented diseases in terms of cause-and-effect relationships among their pathophysiologic states (3). We were especially interested in seeing how experts could justify their decision rules or logic in terms of an underlying model of mechanisms of dysfunction.

Rules for Producing Decisions. At Stanford, Dr. Ted Shortliffe developed a medical consultation system called MYCIN which gives advice on the treatment of infectious disease and uses a representation of knowledge called production rules which has since become very popular in artificial intelligence (4). The main idea behind production rules is that the decision rules of an expert are packaged in modules that can be easily and flexibly reasoned with in various ways with a sophistication that matches that of the human expert.

Rules Relating Manifestations and Diagnosis. Another medical project is CADUCEUS (earlier called DIALOG and INTERNIST), headed by Drs. Jack Myers and Harry Pople at the University of Pittsburgh. This is a very large endeavor which seeks to capture diagnostic knowledge in the entire field of internal medicine (5). It represents diseases in a hierarchic structure, various rules expressing the dependencies between manifestations and diagnostic hypotheses.

Individual Disease "Snapshot." A different approach was taken by a group at MIT (Dr. Peter Szolovits) and Tufts (Drs. William Schwartz and Stephen Pauker). They used a representation of knowledge developed by Minsky at MIT called "frames." In this approach, knowledge is packaged not by modules which represent decision rules, but instead by modules that represent a snapshot "frame" or picture containing all the knowledge about a given disease (6). The frames can be structured and related in various ways for describing, explaining, and reasoning with specific problems.

CASNET

Our own work on CASNET started out by asking, What kind of knowledge do we want to represent in medical decision making? We began with the observations or findings from which inferences about a patient's illness must be made. In building a computer-based model, some data structure must be chosen to describe them. It is usually useful to distinguish between different categories of observations which can be linked to intermediate interpretations, such as pathophysiologic states. These states are conceptual entities or abstractions inferred from the measurements. For instance, a specific measurement of a patient's visual field by perimetry might show a typically glaucomatous pattern of field loss; or a tonometer measurement might indicate an elevated tension in the eye which is probably due to excessive intraocular pressure.

Glaucoma as Model. Initially we developed the CASNET scheme to represent an in-depth model of the mechanisms of glaucoma. We wanted to cover a variety of mechanisms, particularly those that give rise to complex clinical situations for which a general ophthalmologist (who is not a specialist in glaucoma) might find difficulties in either management or diagnosis. In order to make the causal net an interpretive knowledge structure, we established inference links between the observations and the states described to us by the experts, which in turn needed to be abstracted further in terms of diagnostic categories (Fig. 1). These were defined in terms of the pathways of the causal network. For instance, to define angle closure glaucoma, a pathway can be traced linking angle closure to elevated intraocular pressure and thence to cupping of the optic disc and to visual field loss.

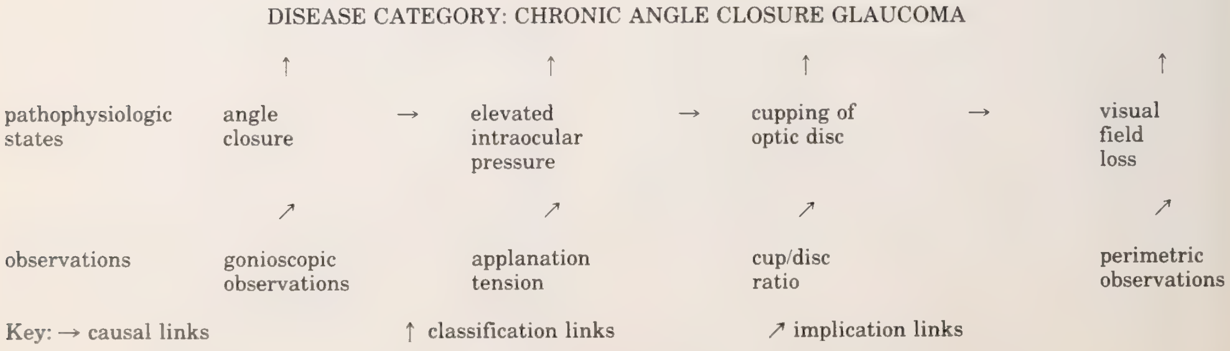

Fig. 1. Adapted from Computers in Biology and Medicine 1978; 8:25–40.

Using this CASNET scheme, we worked with a national network of glaucoma experts and produced a very sophisticated glaucoma reasoning model that was presented at the Academy of Ophthalmology in 1976. The consultation system took part in a panel at which several complex glaucoma cases were discussed. When presented with the same data as the human experts, its conclusions in most aspects matched those given by the experts present (7).

After this experience we wanted to generalize what we had learned, so that we could apply the results to other expert reasoning problems. Some of the lessons we learned were:

- Most AI techniques have an advantage over traditional techniques, mainly because the knowledge base is modular and thus can be easily updated and can provide natural explanations of expert reasoning. Medical knowledge is in a constant state of flux, and one does not want a system in which the findings and conclusions are difficult to modify.
- The reasoning strategies themselves have to be flexible, so that they can indeed perform at an expert level. We are dealing not only with numerical calculations and probabilities but also with what is often called "symbolic reasoning." In other words, we deal with a language of concepts and ways of concatenating these concepts into arguments used by the practitioners in a specialty.
- The programs have to be well-engineered for human use (elegant and clear displays that are easily understood and accessed) or else they will not be successful.
- Once enough experience in building specific expert systems has been accumulated, we must develop general tools for knowledge engineering that will help the practitioner or researcher who has only a modicum of computer training to sit down and build reasoning models. These must be easily run by a general consultation system that knows how to apply various strategies to the reasoning.

Several general frameworks for building expert reasoning models were developed between 1977 and 1980, including ours at Rutgers, called EXPERT (8); the E-MYCIN scheme (9), which is a generalization of MYCIN developed at Stanford; and a number of others, such as KAS/PROSPECTOR (10), OPS (11), and AGE (12).

EXPERT: Adding Empirical Reasoning

The EXPERT system was in part a generalization of CASNET. Causal reasoning alone might be too restrictive in medicine, because in many specialties the mechanisms of dysfunction are as yet not well understood. It seemed reasonable, then, to permit inclusion of a causal interpretation when possible, but to allow reasoning to proceed on the basis of empirical associations when these alone were available. The EXPERT representation that we evolved for describing medical reasoning knowledge then had the following major components:

1. A data structure for organizing the findings, and another for denoting the diagnostic, prognostic, and treatment hypotheses.
2. Reasoning rules stating that, on the basis of a pattern of findings, we can propagate confidence to intermediate hypotheses (such as pathophysiologic states). Since these inferences are typically tentative, they can later (once enough evidence has accumulated) be composed into higher-level diagnostic hypotheses.
3. Rules that focus on a diagnostic hypothesis based on an important pattern of findings, triggering the diagnosis as a possibility without confirming it. These are screening rules, or rules of plausible inference, needed if the model is to capture the scope of reasoning that a human expert has. That is, on the basis of very little data it will still be able to say something.
4. Rules based on patterns of observations that specify direct actions, without any intermediate interpretation. These are often needed if the patient has an acute condition for which symptomatic or emergency treatment is required before reaching a final diagnosis.
5. Rules for reasoning from higher- to lower-level hypotheses, such as those which specify that associated with a particular treatment is a set of possible complications and side effects and a set of contraindications. Another variant of this kind of rule would specify the typical courses of illness associated with a given diagnostic category.

With these data structures we can encode the decision-making rules of the expert, using a type of shorthand as follows:

$$F(T4,0{:}3.2) \rightarrow H(T4D,0.95)$$

This is automatically translated into English statements of the type

If *the finding result of a T4 test lies between 0 and 3.2 mg/dl,*
Then *the hypothesis decreased T4 level suggesting the possibility of hypothyroidism should be given a measure of belief of 0.95.*

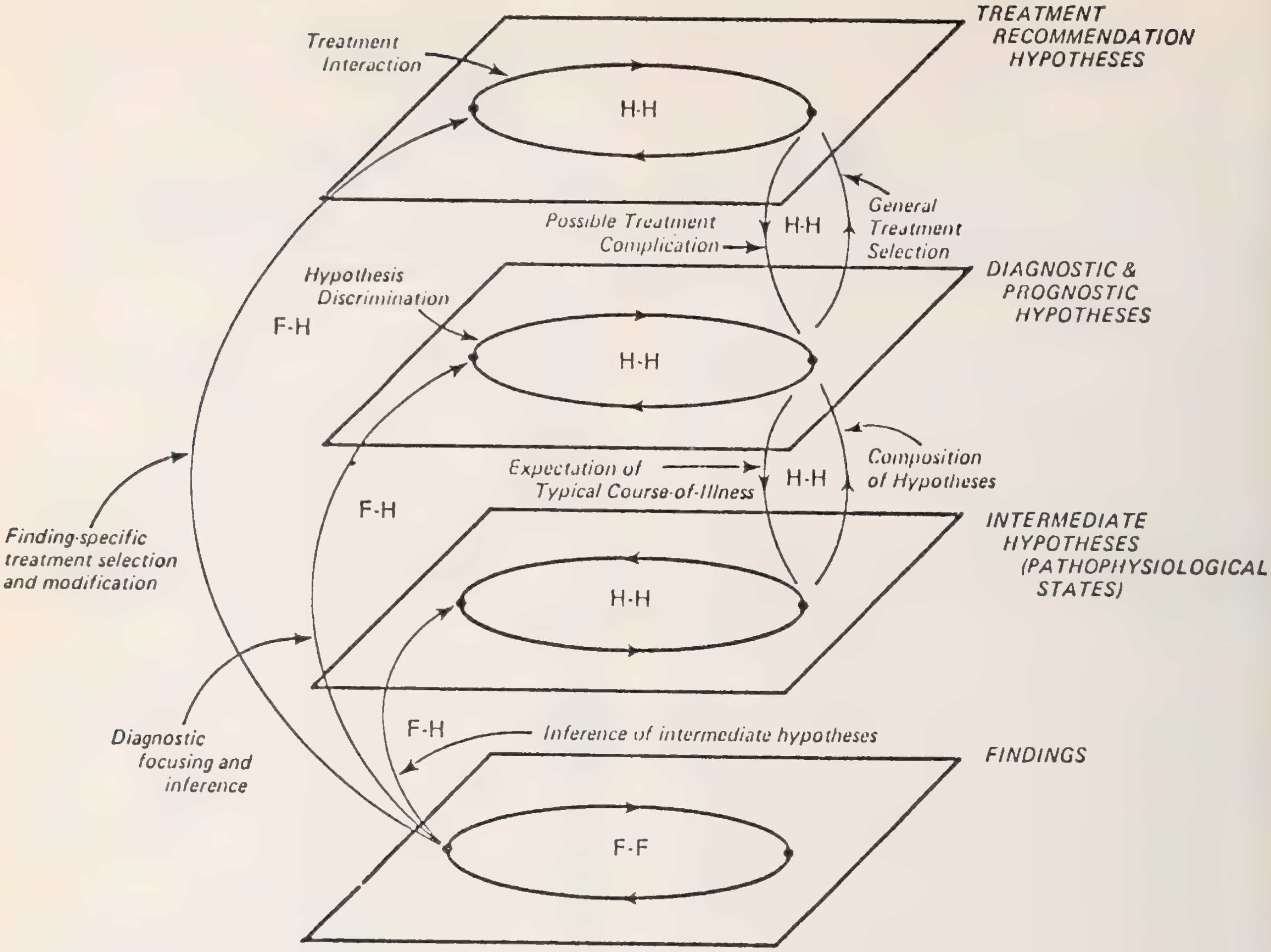
Treatment Interaction
TREATMENT RECOMMENDATION HYPOTHESES
H-H
Possible Treatment Complication
H-H
General Treatment Selection
Hypothesis Discrimination
DIAGNOSTIC & PROGNOSTIC HYPOTHESES
F-H
H-H
Expectation of Typical Course-of-Illness
H-H
Composition of Hypotheses
F-H
Finding-specific treatment selection and modification
INTERMEDIATE HYPOTHESES (PATHOPHYSIOLOGICAL STATES)
H-H
Diagnostic focusing and inference
F-H
Inference of intermediate hypotheses
FINDINGS
F-F

Fig. 2.

This example is a finding-to-hypothesis, or F–H, rule. There are also F–F (finding-to-finding) and H–H (hypothesis-to-hypothesis) rules, as in Figure 2.

When there are many rules to be written, we would like to find ways of summarizing them. We might prefer to use the more classical medical scheme, in which major and minor findings are specified for a disease, and are then used to define the level of confidence in the diagnosis—for example "definite," "probable," or "possible." Taking the major and minor criteria listed in Table as the findings (intermediate hypotheses or combinations of findings) that are needed to

TABLE

Rheumatology Consultant: Levels of Confirmation of Diagnosis by Criteria Needed

Major Criteria	Minor Criteria
1. Swollen hands	1. Myositis, mild
2. Sclerodactyly	2. Anemia
3. Raynaud's phenomenon or esophageal hypomotility	3. Pericarditis
4. Myositis, severe	4. Arthritis < = 6 wks
5. CO diff capacity, nl: <70	5. Pleuritis
	6. Alopecia

	Definite	Probable	Possible
	4 majors	2 majors 2 minors	3 majors
Requirements	Positive RNP antibody	Positive RNP antibody	No requirement
Exclusions	Positive SM antibody	No exclusion	No exclusion

reach a diagnosis. In this example, four major criteria must be present, together with a specific test requirement and the specific exclusion of another test, in order to make the diagnosis at the definite level. To make the diagnosis at the probable level, only two major and two minor criteria must be present. EXPERT can translate a table of this kind into the form of rules described above.

One of the most promising clinical decision-making models now under development is a large-scale consultant in the area of rheumatology, being built by our collaborators at the University of Missouri-Columbia, Drs. Donald Lindberg and Gordon Sharp (13). An example of the output from this particular model is shown in the box.

In the data entry section, the user can prompt the system for the type of problem to be worked on—entering a new case, deleting an old one from a data base, entering a single visit, or retrieving a stored case. Then we can specify whether the case being entered is real or hypothetical, since we don't want to mix these in our data base. Following this, the user enters some other information, and a long set of different findings, organized by the conventions of the field. About 900 findings can be entered for this rheumatology model at present. Any given patient usually has a small subset of these—in the case illustrated, only 31 items.

When the user asks for information, the model, under the control of reasoning strategies in the consultation program, asks only those questions that make sense. That is, it either pursues clues provided by the initial entry of data, or else asks for data that will rule out certain important possibilities or diagnoses.

Once the session has ended, a summary is provided, and the diagnostic interpretations reached are listed by confidence levels. In the example in the box, rheumatoid arthritis (RA) is considered definite; SLE is possible (not ruled out). The model provides a list of findings which if known (though currently unknown) would support the diagnosis of SLE further. This final output or conclusion summarizes a large amount of reasoning inside the model that involved the application of rules from criteria tables like the Table.

**Rheumatology Consultant:
Final Output**

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INTERPRETIVE ANALYSIS
Diagnoses are considered in the categories definite, probable, and possible.

Based on the information provided, the differential diagnosis is

Rheumatoid arthritis (RA)—Definite

Systemic lupus erythematosus (SLE)—Possible

Patient findings consistent with RA:
  Chronic polyarthritis >6 wks.
  RA factor (l.f.), titer 1: <320
  Subcutaneous nodules
  Erosive arthritis

Patient findings not expected with RA:
  Oral/nasal mucosal ulcers

Patient findings consistent with SLE:
  Platelet count, /cmm: < = 99999
  Oral/nasal mucosal ulcers
  Arthritis < = 6 wks, or non-polyarticular

Patient findings not expected with SLE:
  Erosive arthritis

Unknown findings which would support the diagnosis of SLE:
  LE cells
  DNA antibody (hem.)
  DNA antibody (CIEP)
  DNA (hem.), titer 1:
  FANA
  Sm antibody (imm.)

End of diagnostic consultation: 22-Jun-81.
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SEEK

But, what happens when an expert model is not performing as satisfactorily as it ought to, and we wish to improve its performance? To handle this problem our group has developed a system called SEEK (14) which works with the EXPERT program to refine an initial model expressed in the EXPERT form. Our idea was to integrate the performance information from a data base of cases directly into the design of an EXPERT model. The first time the expert sits down with the system he will specify the elements and rules of reasoning, but in any further development, the expert can use SEEK to get advice on how the presumptive diagnoses (or end points) match the diagnoses provided by the initial model. For each misdiagnosed case, SEEK produces an analysis of the type of error. Within a given disease category, it will proceed to the next case, repeating the analysis until all the cases have been exhausted. The net result is that the system has information to provide the model builder, who wants to be shown the different ways in which he can change the reasoning rules so that the net performance for all decisions of a particular disease (such as mixed connective tissue disease) will be displayed. The system will then respond by displaying the 24 cases in which this conclusion did not match the model's conclusions, and propose a number of experiments that ought to improve the performance of the system for these cases. It might tell the user that decreasing the number of major and minor findings in a rule, or deleting the required component in another rule, could improve matters.

We cannot tell a priori which experiment is likely to be the best because when a model is large and complex, the entire data base must be canvassed in order to know precisely how the rules will interact to produce the final decision for each case. The system suggests the experiments by applying certain heuristic rules based on partial empirical performance data. For instance, it will tell the user that if a particular rule had been satisfied, 8 of the currently misdiagnosed cases would have been correctly diagnosed. Further, in this rule the element or component which makes the rule "fail" most often is the number of major components. This suggests decreasing the number of major components in the rule. We call such an operation "generalizing the rule," because the rule antecedents will be satisfied in more cases since they have been logically weakened by decreasing the number of majors required for satisfaction. If this experiment is selected, its impact on performance can be exactly gauged by comparing results after the change with results before the change. In experiments carried out by Politakis and Weiss (17), an initial model which was poor in diagnosis of MCTD was progressively improved without creating any deterioration in performance for any of the other diagnoses.

In rheumatology as in other medical fields there are various degrees of specialization, and it is possible to build a hierarchy of consultation models which can be linked so that a case is handled by the level that is best matched to its own complexity (Fig. 3). An interesting set of artificial intelligence problems arises in investigating how such expert models ought to cooperate with one another in their reasoning. We know this kind of cooperation can be far from easy among human experts, and it remains to be seen what we can learn from our computer models in this regard.

Transfer of Technology

The methods for representing expert reasoning are sufficiently stable to accelerate the development of interpretive reasoning for small decision-making models. With Dr. Robert Galen of the Cleveland Clinic Foundation, we have produced an interpretive model for serum protein electrophoretic results (15). This was a well-circumscribed problem which consisted of analyzing a waveform representing the protein fractions found in blood serum. Once the waveform has been digitized, we must interpret the five fractions in terms of possible underlying infectious mechanisms. How does our expert systems approach to this problem differ from the techniques applied to ECG analysis over the years?

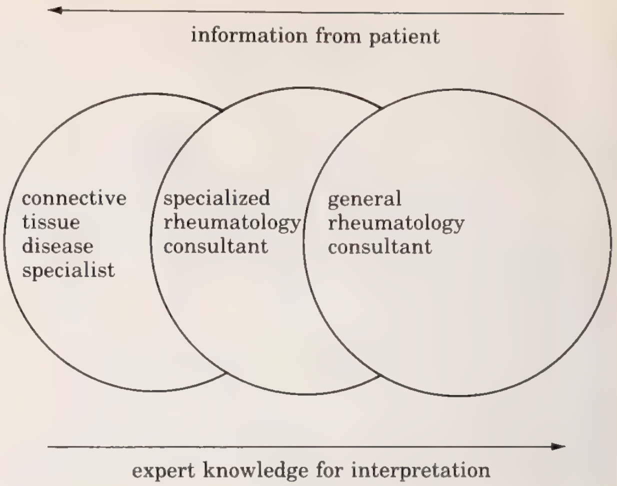
information from patient
connective tissue disease specialist
specialized rheumatology consultant
general rheumatology consultant
expert knowledge for interpretation

Fig. 3.

One important difference comes from the speed possible in developing and testing many versions of an expert model. It took us only 6 months to go from an initial prototype to a final interpretive model that was then evaluated by an expert. Beginning with a very small model with a few conclusions and a single production rule for each, we ended up with a set of 82 reasoning rules and 38 different conclusions. This is a fairly large interpretive model for data consisting of only 5 numbers, the protein fractions.

We tested our system on 256 cases covering the full spectrum of conclusions (16). Subsequently we have seen results from many more cases, and no change in the structure of the model has been needed for correct performance. Such good early results in building a consultation model are unusual and pleasant. In developing the model we were deliberately conservative in not attempting to cover rare problems. For instance, if an M-spike is present, we request the laboratory staff or the pathologist looking at the pattern to decide whether it is an unusual characteristic, rather than trying to perform pattern recognition on it. We could have included such an automatic analysis, but decided against it in order to make the system more acceptable clinically. The result of this work is a model that may look as if it is hand-coded, yet has the ability to rapidly produce new versions. Every time we need to make a change in the rules, we can do so on the large research computer system, run the SEEK system on it until we are satisfied with its performance, and then have the model automatically translated into the assembly language of the microprocessor. We have eliminated the much more painful programming task in assembly language for the microprocessor, which is time consuming and inhibits systematic experimentation.

Summary and Prospects

We now have ways of using the most advanced tools of artificial intelligence and expert systems to build medical reasoning models which can incorporate the latest expertise in a specialty. We can develop them quickly, and we can test variations in the logic of reasoning relatively inexpensively. Although the primary targets are problems of clinical reasoning and research, similar methods and systems can be designed to help in more fundamental research by modeling the interpretation of experiments, providing advice on comparative criteria for evaluation.

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The Computer as a New Basis for Analytic Clinical Practice: Coupling Individual Problems with Medical Knowledge

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As we formulate and solve problems it is not easy to couple medical actions for a unique patient to the best thinking available in the textbooks and journals. In fact, when many variables are involved, common sense and studies in psychology tell us that the unaided human mind cannot rigorously couple thought to action much of the time (1, 2). Passing examinations for knowledge at one time in life, or taking a course in decision-making, cannot alter this basic reality. Nor is it altered by analyses of how the unaided minds of "experts" function. It is true that one human being may be more "expert" than another in solving a complex problem, but that small difference may be irrelevant to what the patient expects and deserves. Let us review what the problem-oriented record in medicine has shown us in this regard, and what some specific new tools can do to help us. Let us then conclude by reviewing the tricks that the unaided mind will play upon us if we persist in current educational methods and examinations and if we continue to encourage the unaided "credentialed" human mind to try the impossible at the time of action.

The problem-oriented system requires and reveals:

1. **A defined data base** from which a complete problem list can be derived for each group of problems. The unaided mind, working with a dictaphone or blank sheet of paper, rarely achieves this first step in a thorough and reliable manner.

2. **A complete list of problems** that accounts for all abnormalities in the data base. Without the guidance of a very rigorous and defined sort, a complete problem list is not achieved in most environments. Frequently, all of the data in the data base are not used to achieve the maximum synthesis that is possible; the unaided mind does not see many of the significant relationships among the various bits of data. And what synthesis there is may be unjustifiably biased by the specialty training and parochial experiences of providers. Furthermore, since a complete list of problems is not made available to all providers on all clinical encounters, medical care activities are not coordinated and cumulative.

3. **Organized planning for each problem** that accounts for (a) other problems and data on the patient; (b) the best known options from the literature for solving the problem; (c) the needs and goals of the patient and his/her family. Time after time it has been observed that the unaided mind using current written records is simply unable to recall all of the necessary data on the patient, unable to keep up to date on all of the options, and unable to integrate them systematically with the patient's personal desires and goals. Indeed the patient's role in his/her own behalf has been grossly neglected (3).

4. **Titled and numbered notes on each problem** that coordinate multiple providers and provide feedback on actions taken. It has been shown repeatedly that there may be no disciplined implementation of a plan once it has been formulated and no intelligent modification of a plan based on

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"Problem-Knowledge Coupler" is a trademark of the PKC Corporation.

additional data. Providers do not communicate effectively and parameters are not followed meticulously and recorded accurately. Clinicians try to deal with many variables extemporaneously, at the time of action, and they frequently fail to do this rigorously.

Concrete Decision-Making

Review of a concrete example illustrates the unreasonable demands on memory and analysis at the time of actually providing care. Suppose a patient consults a physician for a problem such as abdominal pain or hypertension. The patient is likely to expect that the physician carries in memory all of the possible causes, even if there are as many as forty or fifty for a given problem. Certainly a physician cannot identify a cause, or even embark on a search for it, if he or she does not know that it exists, or if he simply doesn't think of it at the time. The patient does not want to believe that his doctor merely thinks of the most probable and never does justice to the unusual case. The patient may further expect that the physician remembers from his education all of the appropriate steps for ruling each cause in or out, and at what cost, benefit and risk, so that all can be discussed honestly and openly with the patient. And finally, if the patient stops to think about it, he may wonder how the physician determines which of the many causes to rule out first. A long list of false tries could be time-consuming, is occasionally dangerous, and is always expensive.

There is a rational basis for deciding which cause to pursue first. Guidance in this regard may be based on many simply obtained facts from the unique individual patient, using the relatively simple tools of history and physical examination, and very elementary laboratory tests that cost little and entail no risk. For each problem, there are 50 to 100 such simple elements; we shall refer to them as "propensities." These are often thought of as the "clinical pearls" of medical practice.

We should pause and remind ourselves that we have already mentioned 200–400 elements that can and should be known to diminish uncertainty in rigorously approaching a single problem. The medical provider may throw up his hands and conclude that he cannot get command of so many details. Should he neglect the details on a unique patient and turn to a sentence in a text on medical decision-making that says: "We argue that a physician should use probabilities to help decide on a strategy for an individual patient" (4)? But probability cannot overcome ignorance; it just makes the best of a situation of ignorance. As the same text notes: "The assignment of probabilities on the case of the individual patient may be viewed as a measure of the decision-maker's ignorance of all the special characteristics of the unique individual."

The thoughtful physician might say to himself, It is true that I cannot handle all the details in my head, but if they are valuable why don't I use the technology to keep track of all the details for me, and thereby diminish uncertainty about the unique individual? After all, the more information we have about a situation, the less probable it is that it is exactly like any other situation; that is why we use the word "unique." Why settle for a suit off the rack, manufactured on the basis of probabilities, if we can have one tailored to our unique physical characteristics no matter how unusual they are?

For this tailoring process in medical practice, we need what I call the "problem-knowledge coupler," that is, a computer program which on the basis of facts obtained from the unique patient, mobilizes information from the literature on a given problem and then presents it to the provider and the patient. Each bit of information on the patient is "coupled" to the relevant bits of information from the literature.

How the Problem-Knowledge Coupler Works

Let us review how the "problem-knowledge coupler" works. Having been presented with the problem, the computer then asks questions about the individual. Each answer then triggers within the computer a translation of positive responses into a list of hypotheses, that is, all possible diagnoses or management strategies suggested by the positive responses. The memory and response time of the machine allow it to consider forty causes or management strategies as reliably as five—something the unaided human mind cannot do. In other words, it will not limit the number of hypotheses that it will consider merely because it cannot remember them all. Nor will it skip some hypotheses because they are rare and not probable. Furthermore, the answers to the early questions do not in any way prematurely halt or direct questions, or bias the computer's responses to later questions.

After asking the necessary 50 to 100 questions about "propensities" relevant to a given problem, the machine will then tally for each cause or management strategy the number of suggestions for each, based on the information (that is, the array of "propensities") obtained from the patient. In seconds, the computer will then confront the patient and the provider with a printout, on the screen or on paper, of the causes or strategies to be considered and the particular characteristics of the particular patient that suggested each. Furthermore, it will enumerate "propensities" and relate them to the total number of "propensities" the machine has stored for each cause or management strategy.

Example: Hypertension. For example, for the problem of hypertension, the computer might print out that this patient manifests 6 out of 7 "propensities" for polycystic kidneys, 1 out of 5 for pheochromocytoma, and so on. Many possible diagnoses, for example coarctation of the aorta, may not appear at all, because that particular patient has none of the propensities, such as diminished or absent femoral pulses, that suggest this lesion.

The user can get further aid from the total computerized problem-oriented system (5, 6) on how to pursue each suggested diagnosis (diagnostic hypothesis) in greater detail. Such an approach helps us find the rare (the highly improbable) diagnosis as securely as the common one (the highly probable).

Excluding Irrelevant Information. In the presence of the problem-knowledge coupler, the user is not electronically overwhelmed with massive amounts of data base information, or with display after display from the entire literature about hypertension or abdominal pain, for example. He/she is confronted only with the literature which is relevant to the unique patient. For example, why should a busy practitioner be burdened with a view of the entire body of the latest information on hypertension associated with licorice-induced hyperaldosteronism, or coarctation of the aorta, if it is inappropriate in the absence of suggestive propensities in his patient? Knowledge overload without time or intellectual capacity to sort it out, leading to "spur of the moment" action, can be as dangerous as ignorance.

The Use of Probability. If after the use of the problem-knowledge coupler uncertainty remains, probabilities and the necessary mathematical calculations can be applied as needed. In many cases, these will not be necessary, because getting command of many simple elements in the aggregate can be extremely powerful in solving problems. With the problem-knowledge coupler we now have the means to do that. And when the problem-knowledge coupler leads to ambiguous and confusing results, the limitations of human experts are not likely to resolve such ambiguities. After all, what we have done is to couple rigorously the findings in a unique patient to what those same experts have painstakingly put into their books and articles about those findings. We have avoided the "voltage drop" based on limited human faculties at the time of action.

Where expert help is needed is in the collecting of reliable data to feed into the problem-knowledge coupler. Its output is only as reliable as the bits of data it receives as input. As with the analyzer in the clinical chemistry laboratory, bad specimens lead to inaccurate results. Reliable outputs from the problem-knowledge coupler can be the basis for studying what in our literature is most discriminatory and productive for solving problems (7). In this respect, the medical librarian is a valuable resource for developing the programs for the problem-knowledge coupler.

Causes of Serious Mistakes. A review of the serious mistakes in medicine, ones for which we have many regrets, shows that many result from losing sight of simple but significant elements. And these simple elements are as powerful for finding the rare as they are for the common. Our oversights often have nothing to do with ignorance of some sophisticated new technique or with inability to apply the very latest in decision theory. Statistics on thousands of medical malpractice cases show that failure to identify or use correctly a simple fact on physical examination was the principal basis for error. In this regard, although the problem-knowledge coupler is just one part of a total computerized problem-oriented system, it is a crucial part in harvesting the full benefits of the analysis of many simple elements in the aggregate.

Limitations of the Unaided Mind

Because we have not articulated more clearly the limitations of the unaided human mind in solving complex problems, we have tended to spin our wheels in medical education, and have wasted enormous resources in medical practice. Some of the traps which the unaided human mind falls into are:

1. Generating hypotheses in the earliest moments of encounters with patients, thereby prematurely biasing the remaining steps in the search for data.

2. Limiting the number of hypotheses generated to a number far smaller than the problem requires. We therefore do not fulfill our responsibility to patients with rare disorders.

3. Generating hypotheses that are more general than the data allow. Crucial findings in a data base will be disregarded. Often the unaided mind will dismiss significant historical facts as mere "clinical suspicion" and pay attention instead to expensive tests that are far less sensitive and specific for solving the problem at hand. As

Wason and Johnson-Laird state, “When the individual mind’s logical ability is restricted, it will operate within heuristic or hit-or-miss procedures which do not guarantee a solution” (1).

4. Neglecting to use the power of low-risk, simple, easy-to-obtain data in the aggregate, the mind tends to proceed prematurely to expensive high-risk procedures.

5. Underestimating the complexity of problems and overinterpreting the data collected. The mind indulges in the categorical reasoning of the expert, which can lead to ordering laboratory tests that are off target, which in turn, as Galen has said, is the main reason that many laboratory tests lack sensitivity and specificity.

6. Allowing probability information based on studies of large populations to supersede highly improbable but correct information based on a unique patient, thereby often getting the patient into trouble. Also, the mind applies inappropriate prevalence data in many of its calculations, giving a patina of quantitative and numerical respectability to a completely misdirected approach.

Confirming or Presupposing Generalization. As Wason and Johnson-Laird (1) have said, We like to think that the educated human mind is capable of thinking in terms of propositions which take into account the possible and the hypothetical, and that this mind will be able to isolate the variables in the problem and subject them to combinatorial analysis which nicely exhausts the possibilities. But this of course, as Wason et al point out, is exactly what most of their subjects failed to do. There is an overwhelming tendency for problem-solvers to verify generalizations instead of trying to falsify them. Problem-solvers even act as if their generalization could not be false: they presuppose its truth, and on top of that, people have a thirst for “confirming redundancy,” always seeing what they want to see, over and over again, by ordering unnecessary tests.

Improving Medical Practice: Organizing Data. Because of these realities, medical practice is not what it should or could be. Furthermore, without better control and understanding of inputs, such as those computerized problem-oriented guidance system makes possible, we do not have reliable feedback on our actions on patients as seen in the broadest context of their lives. This in turn makes inevitable the endless controversies on everything from the value of waiting in an emergency room for amylase levels findings on a person in acute abdominal pain, to the value of Vitamin C in colds and cancer. Unless a finding is as dramatic as children born without arms and legs after the mother has taken thalidomide in pregnancy, a valuable insight is very apt to escape us.

Old and New Pathways in Patient Care

	Old	New
1	Observations on selected patients and basic research	Observations on large populations and basic research
2	Original articles on paper; great variation in standards, form, and means of dissemination	Original articles prepared to more generally accepted standards and disseminated electronically
3	Generation of textbooks, review articles, lectures in medical schools	Generation of electronic guidance tools—particularly diagnostic and management knowledge couplers—for use by patients and providers at time of clinical problem solving; these tools now readily available as affordable microcomputers
4	Extensive and expensive attempts at transferring to minds of students both knowledge and ability to relate it rigorously to unique patients at time of clinical action	Rapid, easy, economical instruction of patients and providers in use of up-to-date guidance tools (as traveler uses up-to-date map without courses and exams in geography and cartography)
5	Complicated credentials system (school examinations, national and specialty boards) to measure limited success of transfer in step 4—all done at one point in time and considered a reliable indicator of future performance, without random checks and discipline on actual performance	Random checks for reliability, thoroughness, and efficiency in use of up-to-date guidance tools; prompt correction of deficiencies or temporary removal of offenders from system (as a bad driver is disciplined within rules of system)
6	Credentialed providers generate medical records; unaided mind elicits data from patients, then integrates it with limited knowledge base that can be recalled and processed at time of action; records often illegible, inconsistent in structure, limited in context	Computerized problem-oriented records generated from computerized histories and physical examinations and knowledge-coupler results
7	Most records never used for study or for feedback on our present notions and hypotheses in medical science	Continuous electronic monitoring and analysis of data in computerized records; proper adjustments made in guidance-system content as results of application of present knowledge become known

Many of the difficult problems now to be solved in medicine are basically problems of information on large numbers of people over long periods of time. But without the right information tools, the situation can degenerate into endless polemics based on inadequate data. After all, amylase determinations and Vitamin C, and an endless list of other laboratory determinations and basic science discoveries, have been around for a long time, and the data involved with their use should have spoken to us long ago. But there is no discipline about the generation and organization of data, so that all we hear are endless dialogues between individuals and prestigious organizations, who base their remarks on studies which are even more provincial in time than in context. Discipline and organization of data are not flashy discoveries in the sense that isolated bits of new knowledge are, and yet without them, the flashy pieces may get out of control and do more harm than good, while the real answers escape us.

Diagnosing Medical Three Mile Islands. There are many more medical Three Mile Islands than we care to admit. What Three Mile Island needed was not more research in theoretical physics. It needed a system to ensure that the ordinary person responsible for decisive action reliably understands what should be done—like turning the proper valve and correctly interpreting the data as it emerges. Neglect of one or two simple observations, as improbable as those observations may appear, can have serious consequences for us all.

Such a reliable system would generate a vast new world of knowledge and technology safer than individual humans can now only vaguely imagine. Medical libraries and librarians would go from passive repository roles to active "coupling" roles in the computerized problem-oriented guidance system for patient care.

In the medical literature an increasing number of articles demonstrate empirically that the unaided mind cannot deal thoroughly and reliably with complex problems at the time of action. Three striking examples: an article from Duke University on antibiotic use (8), an analysis from Harvard on the use of data by physicians in arriving at conclusions (9), and Elstein's book on problem-solving (10).

Educational approaches in which information is "taught" and examinations for retention of that information are given at regular intervals solve nothing. Nor can we assume that we solve anything by superimposing on these efforts an infinite elaboration of detail within a given specialty, such as laboratory medicine or cardiology, each group publishing its own journals, buying its own computer systems, and developing its own new procedures, which others then use unwisely and indiscriminately in far too narrow a context.

Emphasis should shift from communication and development within specialized groups to rigorous communication among all the groups, so that appropriate knowledge is integrated into the unique problem of the moment.

Summary

Unfortunately, many people conclude from this delineation of our failings that we need to teach problem-solving in medical schools, and that more postgraduate education is necessary. The central question is not how you teach a single mind to solve problems better, but what is the best combination of system, machines, and specific types of people for solving any health care problem in the context of an individual patient's life?

Once we see the problem in this way, we expend energy and resources in a very different manner. The switch to new premises and new tools for education (11, 12) and care will not be easy. But once we make the switch, we shall find that powerful tools like the problem-knowledge coupler are useful, even essential, in many areas besides medicine.

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General Articles, Specialty Notes, and Student's Corner

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Cesarean Section Patterns: Influence of a Perinatology Service

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Abstract

We investigated the incidence of and indications for cesarean section in a department 1 year before and after the establishment of a perinatology service. A very significant increase in total cesarean section rate from 14.3% before to 18.5% after establishment of the division was noted ($p = 0.005$). However, a clear change in distribution of indications for cesarean sections was not noted. At the same time, uncorrected perinatal mortality decreased from 21.9/1000 to 19.2/1000 (not statistically significant). The total increase in rate of cesarean section was attributable to the voluntary staff, which prior to the establishment of the perinatology service had much lower rates of cesarean section. This "shock response" was particularly strong among physicians on faculty before establishment of the service. It is concluded that the establishment of a perinatology service in an existing department will affect cesarean section rates significantly. This effect is, however, short-lived and can be remedied with appropriate internal departmental quality control measures.

As reported by the recent National Institutes of Health Consensus Development Conference, the cesarean section birth rate in the United States increased during the 1970s from 5.5% in 1970 to 15.2% in 1978 and appears to continue to rise (1, 2). Cesarean sections have therefore become a focus not only of medical but also of public controversy. Most teaching institutions and even community hospitals (3, 4) today carefully review primary cesarean sections. Such internal peer review within hospitals has been strongly recommended (1, 2). Some observers have also suggested that cesarean section rates may be affected by such additional paramedical factors as defensive medicine, financial incentives, and a trend toward supersubspecialization in obstetric practice (perinatology). Only limited data on these points are available. A preliminary report by this group (4) suggested that organizational changes toward more sophisticated obstetrical care may result in a change in cesarean section pattern within a department. The senior author's responsibility for the complete reorganization of a department presented the unique opportunity to investigate further the influence on cesarean section patterns of the establishment of a perinatology division in a department.

The study presented here suggests that the establishment of a perinatology division does affect practice patterns significantly.

Materials and Methods

Departmental Organization. The Mount Sinai Hospital Medical Center of Chicago is a university-affiliated teaching hospital in the inner city of Chicago. In July 1981 a new departmental chairman was appointed. A full-time faculty covering all three board-approved subspecialities in

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obstetrics and gynecology was recruited, resulting in the establishment of a perinatology division by September 1, 1981. With establishment of the perinatology division, around-the-clock consultation services were made available to the voluntary staff of the department. However, neither consultation rules nor consultation requirements were established.

Prior to the recruitment of the new faculty, the department, including the independent residency program, was supervised by a four-man part-time faculty headed by an acting chairman. None of these four faculty members was board eligible or certified in any of the subspecialities.

After July 1981 a general reorganization of the department took place. Approximately one third of the residents in the independent departmental residency program were exchanged during the first year. Daily teaching rounds were instituted on the obstetrics service. All primary cesarean sections as well as any other obstetrical complications were reviewed in at least one of the weekly subspecialty conferences dedicated to perinatology and/or neonatology. A weekly perinatal conference was established. Detailed monthly perinatal morbidity-mortality statistics were presented in a combined pediatrics-obstetrics conference. Attending physician attendance in the weekly teaching day rose initially precipitously. The initial difficulty encountered with some voluntary staff concerning the open discussion and critique of cases in these departmental conferences was rapidly overcome.

The total number of obstetrical admissions did not increase the first year. However, a marginal shift in admitting pattern could be observed, in that some of the attending physicians who had privileges at various hospitals brought increasing numbers of high-risk patients to Mount Sinai Hospital Medical Center while leaving the low-risk patients at other institutions. This trend was also supported by the establishment of a departmental sonography unit with level II capability.

Study Population. We compared data on cesarean section for the 12-month period of September 1 to August 31 in the years 1980–81 and 1981–82. The earlier 12-month period represented time prior to the establishment of the perinatology division; the subsequent 12-month period represented the initial months of the existence of the division.

All cesarean section births were divided into the standard categories of dystocia, fetal distress, breech, repeat, and "other," as described elsewhere (4). Only the predominant diagnosis was included. Whenever doubt about diagnosis existed, a detailed chart review was performed. Each indication for cesarean section was thus counted only once. All breeches delivered by cesarean section were considered in the breech category even if a trial of labor had preceded the cesarean section. When the diagnoses of dystocia and fetal distress were listed, the individual case was categorized as dystocia unless the infant required admission to the neonatal intensive care unit and had a low Apgar score. Cesarean sections with no clear indication were included in the "other" category.

Statistical analysis was done by the standard chi-square analysis, and the level of significance was set at $\alpha = 0.05$. This statistical analysis was performed by a medical statistician at a different institution (JT).

Results

For the year prior to establishment of our perinatology division, 1,332 patients were recorded in our obstetrical unit (see Table 1). Of those, 191 (14.3%) underwent cesarean sections. In the following year 1,322 deliveries occurred. Of those, 245 (18.5%) underwent cesarean section. The increase in cesarean section rate between the 2 years was statistically highly significant ($p < 0.005$). The increase in total cesarean section rate was not due to a particular cesarean section indication. Although among primary cesarean sections increases in cesarean section indications were observed for the diagnoses of fetal distress (11.6% to 16.2%) and breech (5.8% to 10.2%), no statistically significant pattern could be recognized. A decrease was noted in the dystocia diagnosis (from 26% to 21.2%), which also was not

TABLE 1
Study Population

	1980–81	1981–82
No. of deliveries	1332	1322
No. of cesareans	191 (14.3%)	245 (18.5%)*
Primary c. section	113 (59.2%)	156 (63.7%)†
Fetal distress	22 (11.6%)	40 (16.2%)
Dystocia	50 (26%)	52 (21.2%)
Breech	11 (5.8%)	25 (10.2%)
Other	23 (12%)	28 (11.4%)
Medical	7 (3.6%)	11 (4.5%)
Repeat cesarean	78 (41%)	89 (36.5%)

Distributions of primary cesarean section indications in the two time periods were not significantly different.

* Increase significant at $p < 0.005$.

† Not significant.

statistically significant. All the other indications remained rather stable.

We analyzed cesarean section incidence per month of study year, by total cesarean section rate (Fig. 1) and breakdown by indication for primary cesarean sections (Fig. 2). Clearly, the increase in departmental cesarean section rate was randomly distributed over the year 1981–82 and not clustered in an initial period.

With establishment of the perinatology division, a teaching service was also established. This service comprised all obstetrical patients under the responsibility of the full-time faculty, not only private patients managed solely by the perinatologists. Private patients of other full-time physicians in the group were also included. Of 1,322 patients who delivered in our department during the year 1981–82, 723 were delivered by private attendings; 599 were delivered under the supervision of the new full-time group (Table 2). The cesarean rate on the private service was 22%, whereas the cesarean section rate on the teaching service was 14.4% (Table 2). This difference was again highly statistically significant ($p < 0.001$). Most interesting, the cesarean section rate for the teaching service was identical to the cesarean section rate for the whole department prior to the establishment of the perinatology division, and cesarean section rates for the whole department in 1980–81 were statistically very different from deliveries on the private service during 1981–82 ($p < 0.001$).

Major indication for cesarean section is related to the total number of deliveries as a rate per 100 deliveries in Table 3. The percentage of increase owing to an indication was calculated by the method of Bottoms et al. (5) using the following formula: (increase in rate for indication × 100)/total increase in rate.

The distribution of cesarean sections by indication did not change significantly for either the total service or the private service alone. The increase in total cesarean section rate for the department was largely due to increases in repeat cesarean section, fetal distress, and breech indications. Small increases were noted for all the other indications as well; however, they were clearly less important. None of the cesarean section increases alone proved statistically significant. It is again clearly apparent, however, that the increases in cesarean section rates were due to increases on the private service.

Table 4 summarizes the delivery pattern of

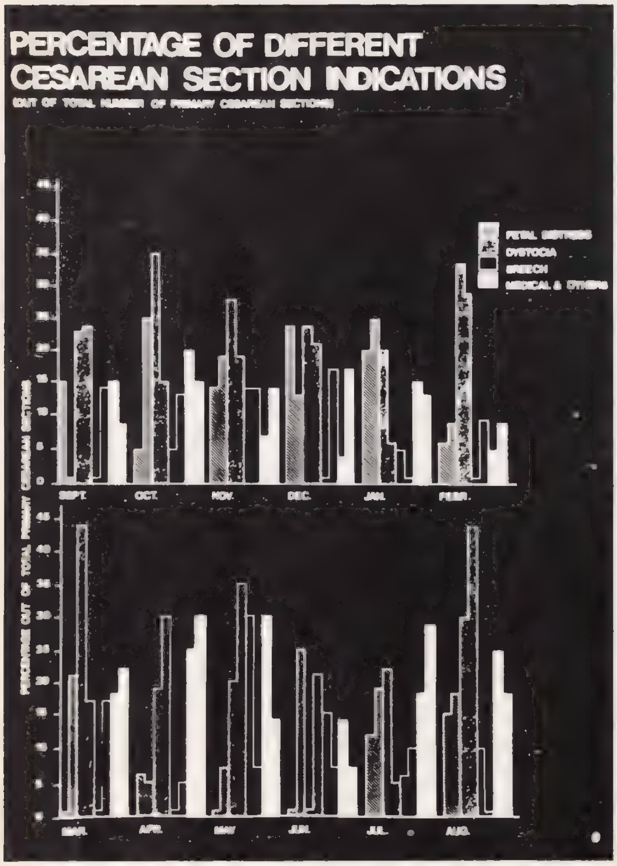

Fig. 1. Percentage of total cesarean sections per month. Figure indicates rather random distribution of cesarean section rate increase over study period 1981–82. Only month of August 1982, last month of second study period, showed decrease in cesarean section rate (from 14.7% to 9%). This observation may, in fact, represent the beginning of the corrective trend in departmental cesarean section rates which was clearly recognized for the 4-month period following the study between September and December 1982.

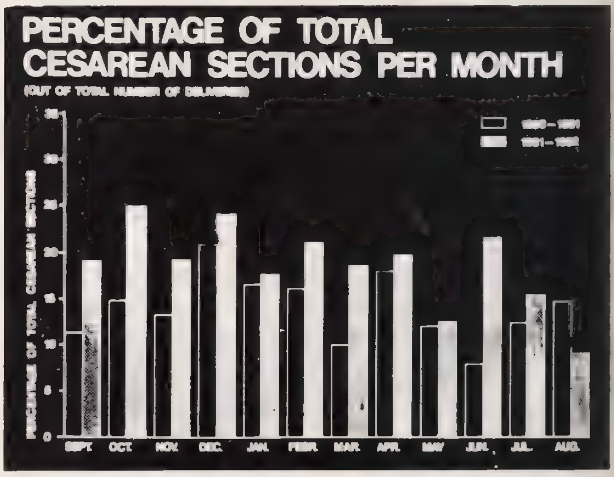

Fig. 2. Indication for cesarean section as percentage of total number of primary cesarean sections. First half of each bar represents percentage of cesarean section indications for 1980–81; second half represents study year 1981–82. Indication patterns vary over the two study years rather at random. Because of small numbers in each group, "medical" and "other" indications were combined for this graph.

TABLE 2

Cesarean Section Incidence per Service

	1980–81	1981–82
Private service		
deliveries	1332	723
cesareans	191 (14.4%)*	159 (22%)*
Teaching service		
deliveries	—	599
cesareans	—	86 (14.4%)*

No significant differences between cesarean sections in private service 1980–81 and teaching service 1981–82 were noted.

* $p < 0.001$.

those ten voluntary attendings who practiced in the department in both investigated years. The increase in cesarean section rate was a constant one for all attending physicians. Most interestingly, however, the two largest increases in cesarean section rate were encountered with two attendings who had previously been faculty. The four physicians who represented faculty in 1980–81 more than doubled their cesarean section rates in the second year of our study.

The evaluation of changes in perinatal mortality and morbidity proved difficult because of major changes in statistical record-keeping introduced after September 1, 1981. Although individual parameters of morbidity could thus not be compared, the uncorrected perinatal mortality rate for our study population decreased from 21.9/1000 in 1980–81 to 19.2/1000 in 1981–82. This decrease was, however, statistically not significant.

Discussion

The reorganization of our department presented a unique opportunity to investigate the influence of the establishment of a perinatology service on patterns of cesarean section. The findings in this study indicate that the establishment of a perinatology division clearly does influence these patterns. We observed a statistically highly significant increase in total number of cesarean sections in the first 12 months after establishment of the division, an increase not related to any single indication for cesarean section. Although the total percentage of repeat cesarean sections did increase, the relative incidence of repeat cesarean sections within the pool of cesarean sections decreased.

This study thus confirms our earlier preliminary suggestions (4) that the establishment of a perinatology division may influence patterns of cesarean section for a whole department. The influence observed in this study was, however, different from the one described in our earlier publication. There, the primary cause of increase in cesarean section rates between 2 years was dystocia, not an important factor in our study presented here. The percentage of increase in cesarean section due to breech presentation was twice that observed in this study whereas fetal distress as an indication for cesarean section did in fact decrease (4). In our study presented here fetal distress represented one of the reasons for the observed increase in rate of cesarean section.

Organizational changes in an obstetrical unit may thus affect the pattern of obstetrical practice in different ways. The particular change in patterns of practice observed in this study did not come as a surprise and may, in fact, at least partially represent new diagnostic criteria established with the creation of the perinatology division. Thus, for example, the diagnosis of dystocia was no longer made unless internal pressure transducers were in place to confirm appropriate

TABLE 3

Cesarean Section Indications and Total Number of Deliveries as Rate per 100 Deliveries

Cesarean Indication	1980–81	1981–82, Total Service/Private Service	% of Increase* Total Service/Private Service
Repeat	5.85	6.73/8.43	21/34
Fetal distress	1.65	3.02/3.32	32.6/22
Dystocia	3.75	3.93/4.56	4.3/11
Breech	0.82	1.89/2.63	25.5/24
Other	1.73	2.12/2.07	9.3/4
Medical	0.52	0.83/0.97	7.4/6
Total	14.32	18.52/21.98	

Distributions of cesarean section indications on either total or private service were not different from those of the total service in 1980–81.

* Calculated according to Bottoms' formula (4).

TABLE 4
Cesarean Section Rates of Ten Voluntary Attendings in Both Years

Attending	1980–81		1981–82		% Change*
	Deliveries	Cesarean No. (%)	Deliveries	Cesarean No. (%)	
A	70	16 (22.8)	51	16 (31.3)	+37
B†	136	19 (13.2)	34	8 (23.5)	+78
C†	214	18 (8.8)	51	14 (27.6)	+21
D	258	31 (12.0)	243	40 (16.5)	+37
E	52	8 (15.4)	50	9 (18)	+17
F	79	11 (14)	94	26 (27.6)	+97
G†	187	26 (13.9)	10	5 (50)	+26
H†	107	20 (18.7)	36	10 (27.8)	+49
I‡	78	15 (19.2)	80	23 (28.7)	+50
J	10	1 (10)	71	8 (11.2)	+12

* Calculated according to Bottoms' formula (4).

† One of the four physicians who in 1980–81 directed the department. The combined rate of the four increased from 14.15% to 32.22% ($p < 0.001$).

‡ Denotes group of physicians.

uterine contraction patterns for adequate periods before the diagnosis of dystocia was made. Also, fetal scalp blood pH assessment was introduced to the labor floor as a daily routine in the assessment of fetal distress. These and other changes in practice became feasible only because of purchase of major new equipment for the labor floor.

The most surprising aspect of this study was the recognition that the increase in total cesarean section rate was entirely due to the practice of voluntary staff, which previously had a much lower rate. Patients managed by full-time faculty, both perinatologists and others, had in fact a cesarean section rate identical to that of the whole department prior to the establishment of the perinatology division. This observation indicates a "shock response" by the voluntary staff to the establishment of new policies in the department. Nothing exemplifies this "shock response" better than the fact that some of the highest increases in cesarean section rates occurred among physicians who previously had been faculty in the department and had rather low cesarean section rates. We thus identified a previously unidentified physician-related factor that may influence cesarean section rates which must be considered along with other factors recognized earlier as predisposing to physician bias (3, 4, 6–8).

Although this "shock response" came as a surprise, immediate remedial action was taken once it was recognized. The new faculty assumed responsibility for the cesarean section rate increase based on the argument that the new policies, procedures, and clinical management patterns had not been accompanied by proper training, explanation, teaching support, and supervision. After a renewed educational drive and the establishment of new policies, such as reemphasis of second-opinion requirements, mandatory cord blood pH measurements in all cases of cesarean sections with a diagnosis of fetal distress, and more second-opinion utilization, the total cesarean section rate for the subsequent months of 1982 was reduced to less than 13% for the whole department. The primary cesarean section rate in that period was always less than 8.5%. With these changes, the cesarean section rate thus returned to a level almost identical to that in the year prior to the establishment of the perinatology division.

This study thus confirms preliminary results of our earlier report and expands on the explanation (4). The institution of significant changes in obstetrics practice in an academic setting will not necessarily lead to a long-lasting increase in cesarean section rate but may significantly affect short-term rates. Immediate effects on practice patterns must be carefully monitored to prevent them from becoming permanent. Our earlier report indicated that although overall cesarean section rates will not be affected in the long range, the distribution of indications for cesarean section may change with the establishment of a perinatology division (4). A change in distribution of individual cesarean section indications could not be confirmed in this study. The lack of such a statistically significant change may be due to the smaller number of patients in this study, and consequently any such effect is not ruled out. However, the recognition that major changes in departmental practice patterns may be the result of organizational changes in the department should be acknowledged, and appropriate departmental quality control measures must be taken to prevent unnecessary increases in cesarean section patterns even if transient. It should, however, also be acknowledged that only a major reorganization of departmental practice patterns will at times lead to improvement in perinatal morbidity and mortality. Further investigations of paramedical factors influencing cesarean section rates are urgently needed in order to decrease unacceptably high cesarean section rates in the United States (9).

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Optimal Delivery of Nonvertex Twins

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Abstract

Ninety-four twin deliveries with breech-presented fetuses were reviewed. Vaginally delivered infants had 9.4% perinatal morbidity. Two thirds of the morbid fetuses were delivered with internal version or full breech extraction, or both. Fifteen percent of the breech twins were delivered abdominally without perinatal morbidity. Twin number (first or second) and delivery mode did not correlate with birthweight, Apgar scores, or perinatal morbidity. Two thirds of the depressed newborns were premature fetuses, first or second breech-breech twins. Cesarean section is probably the recommended mode of delivery for breech-breech and less-than-2500-gm breech twins.

The optimal mode of delivery of breech twins is controversial. Fetal loss in twin gestation is triple the rate for singleton pregnancies (1). Many obstetricians prefer cesarean section whenever one or both twins are breech-presented (2, 3). Cesarean section reduces mortality in fetuses weighing less than 1500 gm (3). However, perinatal morbidity and neurologic damage in breech fetuses weighing less than 1500 gm are similar in abdominally and vaginally delivered infants (4). Internal version and full breech extraction of twins weighing less than 1500 gm frequently resulted in neurologic damage and asphyxia (5).

This study was undertaken to correlate fetal birth weight, Apgar scores, and morbidity with delivery mode and twin number in breech-presented twins.

Materials and Methods

Ninety-four twin breech deliveries were evaluated from 1976 to 1980. Vertex-vertex twins and fetuses weighing less than 1000 gm were excluded. In this study time interval, obstetric management, departmental policy, and cesarean section rates remained uniform. The infants were followed from delivery to the age of 1 month.

Suspected twin pregnancy was confirmed by sonography and in a few cases by plain abdominal X-ray. Whenever preterm labor was imminent, beta-sympathomimetic tocolytic agents were administered along with glucocorticoids to enhance fetal pulmonary maturation. General anesthesia and uterine muscle relaxants were rarely used. Internal version and breech extraction were usually performed under epidural anesthesia.

Multiway frequency tables were obtained. Number of breech twin (first or second), mode of delivery (vaginal or cesarean section), and fetal birthweight were compared with 1- and 5-min Apgar scores and perinatal morbidity (respiratory distress syndrome, nervous system trauma, musculoskeletal trauma, hyperbilirubinemia). The data were analyzed with the Pearson chi-square test.

Results

Ninety-four parturients with twin gestation and 187 live fetuses were reviewed. One stillborn nonmalformed second twin was not included. Vertex-vertex presentation twins and fetuses weighing less than 1000 gm were excluded. Twin-breech fetuses were distributed in almost equal groups: 34 (36%) parturients with breech-vertex

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presentation, 31 (33%) vertex-breech, and 29 (31%) breech-breech pairs of twins.

Ten (11%) parturients with twin gestation were diagnosed in active labor and 84 (89%) in the second and third trimesters of pregnancy. Fourteen (15%) parturients delivered abdominally without any morbidity. One infant weighing 1300 gm, delivered abdominally, had an Apgar score of 5 at 1 min (Fig. 1). Fifteen morbid infants (Table 1) are presented by birthweight, twin number, fetal morbidity, Apgar scores, and mode of vaginal delivery. Two thirds of these vaginally born infants (10/15) were premature. Respiratory distress of the newborn was noted in six of the premature twins (60%). Seven fetuses (47%) had asphyxia. Nine of the morbid fetuses were second twins (*p* value nonsignificant), and ten (66%) were delivered with internal version and/or breech extraction.

Two neonatal deaths were noted. A 2550-gm second twin was delivered with internal version and breech extraction. The infant had 7–10 Apgar scores but deteriorated quickly, and massive subarachnoid hemorrhage was diagnosed. The second, 1280-gm infant had severe hyaline membrane disease complicated by bilateral pneumothorax (Table 1, patients 3 and 11).

Association analysis of twin number (first or second twin), delivery mode (vaginal or abdominal), fetal birthweight, 1- and 5-min Apgar scores, and fetal morbidity showed that the only interdependent variables were fetal birthweight, 1- and 5-min Apgar scores, and fetal morbidity ($p < 0.001$ for Apgar scores by birthweight and $p < 0.01$ for fetal morbidity by birthweight). Twin number did not correlate with birthweight, Apgar scores, and fetal morbidity.

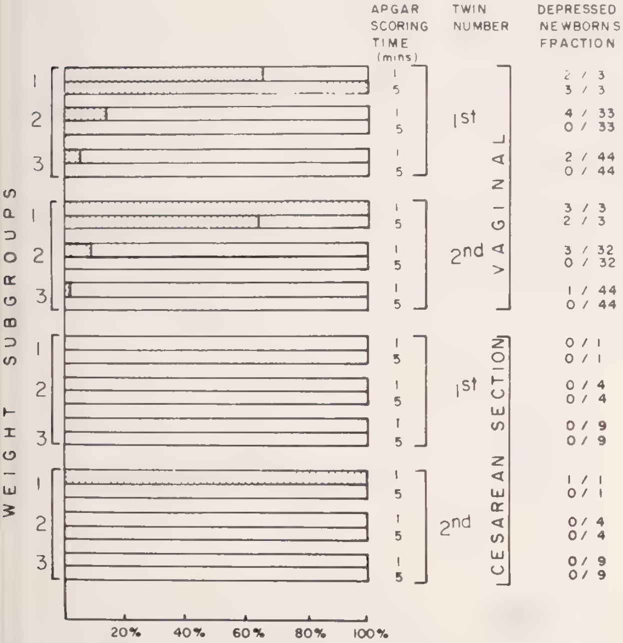

Fig. 1. One- and five-minute Apgar scores of 187 twin breech infants. Dark columns represent percent of newborns with Apgar scores of less than 7. Infants are grouped according to birthweight: 1 = 1000–1499, 2 = 1500–2499, 3 = 2500 or more gm.

Discussion

Intrapartum management of the nonvertex breech twin is controversial. Some authors state that cesarean section is the method of choice for delivery of twins if the second twin is in breech presentation (6, 7). Earlier reports found that breech twins fared as well as vertex; therefore, it was concluded that regardless of presentation a breech twin is not an indication for cesarean section (8, 9). Twin breech presentation was associated with increased mortality regardless of birth order; however, correction for birthweight largely obviated the differences (10). Recent reports concluded that for birthweight of more than 1500 gm routine cesarean section for breech twins may not be necessary (5).

Pitfalls in interpretation of the data available include variations in individual skill and judgment, the isolated choice of the delivery route, the perinatal team, and changing policies during the study time. Twin breech infants weighing less than 1000 gm were excluded because this birthweight group deserves special attention on a large sample basis. Earlier reports stated that perinatal death rate for breech twins weighing less than 1000 gm is 100% (3). In the early 1970s the perinatal death rate for this group was reported to be 59.4% (10) and in a recent study 40.6% for fetuses weighing less than 1500 gm (5). Moreover, most of the traumatic perinatal morbidity appears to occur in the less-than-1500-gm newborns (5, 10, 11).

In this series two thirds of the morbid newborns weighed less than 2500 gm and 27% weighed 1000–1500 gm. Association analysis revealed statistically significant correlation between birthweight, Apgar scores, and perinatal morbidity. Two thirds of the morbid infants were delivered with internal version and/or full breech extraction.

It seems that traumatic vaginal delivery accounts for most of the perinatal twin morbidity, especially in the premature infants. Abdominal delivery for breech infants of less than 2500 gm may reduce some of the perinatal morbidity and mortality. However, this recommendation must be carefully reevaluated in the future because

TABLE 1
Complications Following Vaginal Delivery in 15 Twin Breech Infants

No.	Presentation	Weight (gm)	Twin No.	Apgar scoring	Fetal morbidity	Mode of delivery
1	B–B	1350	2	6–10	RDS	+ FBE
2	B–B	1770	1	6–10	RDS	ABD
3	B–B	1280	1	4–7	RDS (exitus)	IVN + FBE
4	B–B	1356	2	7–9	RDS	+ FBE
5	B–B	1600	1	7–9	RDS	+ FBE
6	B–B	1450	1	4–9	Asphyxia	ABD
7	V–B	1770	2	2–7	Severe asphyxia	IVN + FBE
8	B–B	2500	2	10–10	RDS	IVN + FBE
9	V–B	2320	1	5–8	Asphyxia	Forceps
10	V–B	1600	2	1–8	Asphyxia	ABD
11	B–V	2550	2	7–10	Subarachnoid hemorrhage (exitus)	IVN + FBE
12	B–B	2580	1	4–8	Asphyxia	+ FBE
13	B–B	2320	2	7–10	Asphyxia	IVN + FBE
14	V–B	3200	2	10–10	Hyperbilirubinemia ABO incompatibility	ABD
15	V–B	3400	2	6–10	Asphyxia	IVN + FBE

ABD, assisted breech delivery; FBE, full breech extraction; IVN, internal version; RDS, respiratory distress syndrome of the newborn.

there are several ways to avoid traumatic delivery. Sonographic assessment of fetal head attitude, estimation of fetal weight, and demonstration of the exact location of the ankles can facilitate breech extractions and avoid unnecessary intrauterine manipulations (5).

The common belief that the second twin is smaller and more frequently compromised was not supported by some authors (12). However, the crude mortality rate of twin A was 6.1% versus 8.5% for twin B (13), a finding documented by others (14). Sometimes fetal distress of the second twin may result in a cesarean section after vaginal delivery of the first twin (15). Our data did not suggest any significant differences between twin A and B. Therefore, the same indications for cesarean section for both first and second twins may be applied (16). Careful sonographic evaluation of the twins is mandatory because an early diagnosis in labor of more than 500 gm difference in birthweight between the twins is suggestive of twin-to-twin transfusion or inadequate blood supply to the smaller one. Monoamniotic twins are also theoretically at increased risk of cord accidents. Cesarean section should be liberally used in those cases with individualization of the decision process.

Breech-breech twins are usually delivered abdominally. In this series two thirds of the morbid fetuses were double breech twins, although distribution of twin presentations was uniform: one third were breech-breech, one third vertex-breech, and one third breech-vertex. Therefore, it is probably advisable to deliver these twins abdominally and avoid the hazards of vaginal breech delivery even if estimated birthweight is more than 1500 gm.

Apgar scores and perinatal morbidity are poor prognostic indicators of the long-term performance of the infants. However, these parameters reflect the condition of the infant at birth and, in conjunction with cord blood gases, may be used for immediate assessment of fetal asphyxia. A revolution in the management of second breech twins was suggested utilizing intrapartum, sonographically controlled, external cephalic version (17). If successful, a vertex vaginal delivery may result and the hazards of full breech extraction or cesarean section would be avoided.

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Amniotic Fluid Microviscosity Analysis in Diabetic Pregnancies: Comparison with Other Methods of Lung Maturity Assessment Using Predictive Value Analyses

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Abstract

Three methods employed in fetal lung maturity assessment were compared in predicting the likelihood of neonatal respiratory distress syndrome (RDS) in pregnancies complicated by diabetes and erythroblastotic disease. The techniques employed were L/S ratio determinations, presence or absence of phosphatidylglycerol, a stabilizer of surfactant, and fluorescence polarization. The latter technique assesses the surface-tension lowering activity of the lipid micelles in amniotic fluid and is dependent upon the total surface-active lowering properties of phospholipids found in fetal lung secretions.

Amniotic fluid analyses were performed in 57 pregnancies including 11 known diabetic patients and 3 with known Rh^- incompatibility. In the 10 pregnancies associated with neonatal RDS, L/S ratios were significantly lower (2.6 ± 0.9 vs 5.1 ± 0.5, $p < 0.02$) and fluorescence polarization levels higher (0.344 ± 0.007 vs 0.312 ± 0.005, $p < 0.001$) than in unaffected pregnancies. Whereas diabetic subjects had L/S levels comparable to normal, their FP values were significantly higher than in age-matched normal pregnancies (0.331 ± 0.009 vs 0.292 ± 0.009, $p < 0.01$). The incidence of RDS in diabetic pregnancies was also significantly higher in pregnancies complicated by diabetes ($\chi^2 = 3.98$, $p < 0.05$) or Rh incompatibility ($\chi^2 = 5.92$, $p < 0.025$).

RDS has been shown to occur in diabetic pregnancies despite the finding of mature L/S ratios. The results of this study would suggest that despite the presence of normal L/S ratios, amniotic fluid from diabetic pregnancies does not have the normal surface tension lowering properties seen in unaffected pregnancies. We conclude that fluorescence polarization is a highly sensitive method in the prediction of RDS. As it can be performed very quickly, it is the single best screening test for use in managing of complicated pregnancies.

Diabetic pregnancies have an increased incidence of respiratory distress syndrome (RDS) in the newborn (1). Totally reliable prediction of the likelihood of RDS has not been possible using lecithin/sphingomyelin ratio (L/S) on amniotic fluid samples obtained from diabetic subjects immediately prior to delivery (2, 3).

RDS occurs when there is an absolute reduction in lung surfactant (4). This secretory product of alveolar metabolism promotes stability of the alveolus during ventilation by reducing the surface tension thereby preventing atelectasis. The surface-tension lowering properties of surfactant are attributable to the presence of both disaturated phosphatidylcholine (DSPC), the major phospholipid species found, and stabilization of surfactant by relatively small amounts of an acidic phospha-

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tide, phosphatidyl glycerol (PG) (5, 6). The presence of one or both of these substances has been shown to correlate better with neonatal outcome than L/S ratio in both normal and diabetic pregnancies (7, 8).

Measurement of the actual surface tension lowering properties of lung secretions in amniotic fluid should provide a better estimate of the likelihood of RDS. An empirical relationship exists between the surface tension of fluids and their intrinsic microviscosity (MV). Shinitzky first showed that measurement of fluorescence-polarization (FP) of the lipophilic dye probe, diphenyl hexatriene, was able to be correlated with the microviscosity (MV) behavior of these fluids (9). Subsequently, he and others have shown that FP-MV measurements of amniotic fluid are reliable indicators of fetal lung maturity and can predict neonatal outcome (10–12).

The purpose of these studies was to compare the technique of FP-MV of amniotic fluid samples, obtained from a series of high-risk pregnancies, with L/S ratio and PG determinations in predicting neonatal outcome and RDS. The data suggest that FP-MV is a highly sensitive technique for assessing fetal lung maturity especially during antepartum management of diabetic pregnancy.

Materials and Methods

Apparatus. Elscint Mv 1-a microviscosimeter (Elscint Co., Hackensack, NJ 07602).

Reagents. 1,6 diphenyl 1,3,5 hexatriene (DPH) in tetrahydrofuran (Item MV-101, Elscint Corp. Hackensack, NJ 07602). Silica gel plates (E. Merck, Darmstadt, W. Germany). Chloroform, methyl alcohol, acetone, boric acid, sodium bicarbonate, sodium hydroxide, bromothymol blue (E. J. Baker Chemical Company).

Patient Population. Eleven pregnant diabetics, classes B-D (1), and 3 patients with pregnancies of Rh incompatibility were studied and compared to 43 normal pregnancies. Amniocenteses were performed for medical indications (e.g. caesarean section), usually within 24 hours of delivery. Samples contaminated with blood or meconium were not used. Samples were assayed within 2 hours of collection. Determination of L/S ratios of amniotic fluid samples was performed following extraction with chloroform/methanol as described by Borer (13).

The presence or absence of phosphatidylglycerol (PG) in amniotic fluid samples was determined following one-dimensional thin layer chromatography as described previously (14).

Determination of FP-MV was performed on unextracted samples following centrifugation of 1600 RPM to remove cellular debris. The procedure used has been described by others (15, 16) and is presented only briefly here. One ml of amniotic fluid was added to 1 ml phosphate buffered saline (pH 7.4) containing 2×10^{-3} M DPH and the mixture was vortexed vigorously. Samples were incubated for 30 min at 37°C in a water bath and then cooled to 24°C. FP-MV was determined at 24°C using an Elscint MV-1 microviscosimeter. The fluorescence-polarization value was derived from the equation

$$\text{FP-MV} = \frac{I_{//} - I_{/}}{I_{11} + I_{/}}$$

where I_{11} and $I_{/}$ are respectively the light intensities emerging parallel and perpendicular to the original light source. FP is provided by direct readout from the instrument (9).

The presence of respiratory distress syndrome (RDS) or transient tachypnea of the newborn (TTN) was determined by an experienced neonatologist. The criteria for RDS included (a) the onset within 2 hours of birth; (b) chest x-ray with reticuologranular pattern and air bronchogram; (c) hypoxemia requiring ventilation support. The diagnosis of TTN was based on the presence of (a) onset within first 2 hours of life; (b) chest x-ray compatible with increased fluid retention in vascular spaces of the lung; (c) resolution within days without requiring ventilatory support. Statistical analyses were performed using the Student's *t*-test for unpaired samples or chi-square analyses where indicated. Significance was accepted at levels of 5% or less. Analyses of the data using Bayes theorem provided indices of sensitivity, specificity and predictive value for all tests in this patient population (15).

Results

In our study of 57 pregnancies, 10 infants developed respiratory distress syndrome. Of the affected infants, 4 were offspring of diabetic pregnancies and 2 had Rh^- incompatibility with mild to moderate erythroblastosis. Chi-square analysis of these data confirmed previous observations that there was a significant risk of RDS in diabetic ($\chi^2 = 3.98, p < 0.05$) and Rh^- incompatible pregnancies ($\chi^2 = 5.92, p < 0.025$).

We compared the values obtained for L/S ratio with fluorescence-polarization determinations from amniotic fluid samples from normal pregnancies and those complicated by RDS (Table 1).

TABLE 1

	N	FP-MV	L/S	PG+/−
Normal, all subjects	45	.312 ± .005	5.1 ± .05	18/12
Normal, >34 wks gestation	11	.292 ± .009	5.9 ± 1.5	
Diabetic	10	.331 ± .009*	5.0 ± 0.6	4/1
Rh(−) incompatibility	3	.360 ± .012***	2.8 ± 0.4***	1/2
RDS	10	.344 ± .007***	2.6 ± 0.9**	3/5

* $p < 0.01$ vs normal
** $p < 0.02$ vs normal
*** $p < 0.001$ vs normal

Pregnancies complicated by RDS showed significantly lower L/S ratios ($p < 0.02$) and higher fluorescence-polarization (FP-MV) values than normal ($p < 0.001$). Diabetic pregnancies showed significantly higher fluorescence-polarization (FP-MV) values than for normal gestational age-matched pregnancies ($p < 0.01$) although L/S ratios were not significantly different. Samples from pregnant subjects with Rh$^-$ incompatibility demonstrated significantly higher fluorescence-polarization (FP-MV) values than normal ($p < 0.001$), L/S ratio values were also significantly less mature than normal ($p < 0.001$) in this group.

The contribution to the intrinsic viscosity of surfactant made by phosphatidylglycerol (PG) was examined by comparing mean FP-MV values for samples with and without detectable PG. Amniotic fluid samples containing PG had a mean FP-MV value of 0.308 ± .007 (n = 20), which was significantly lower ($p < 0.005$) than the mean FP-MV value of 0.346 ± .009 (n = 14) for those samples without detectable PG.

The relationships between FP-MV values and

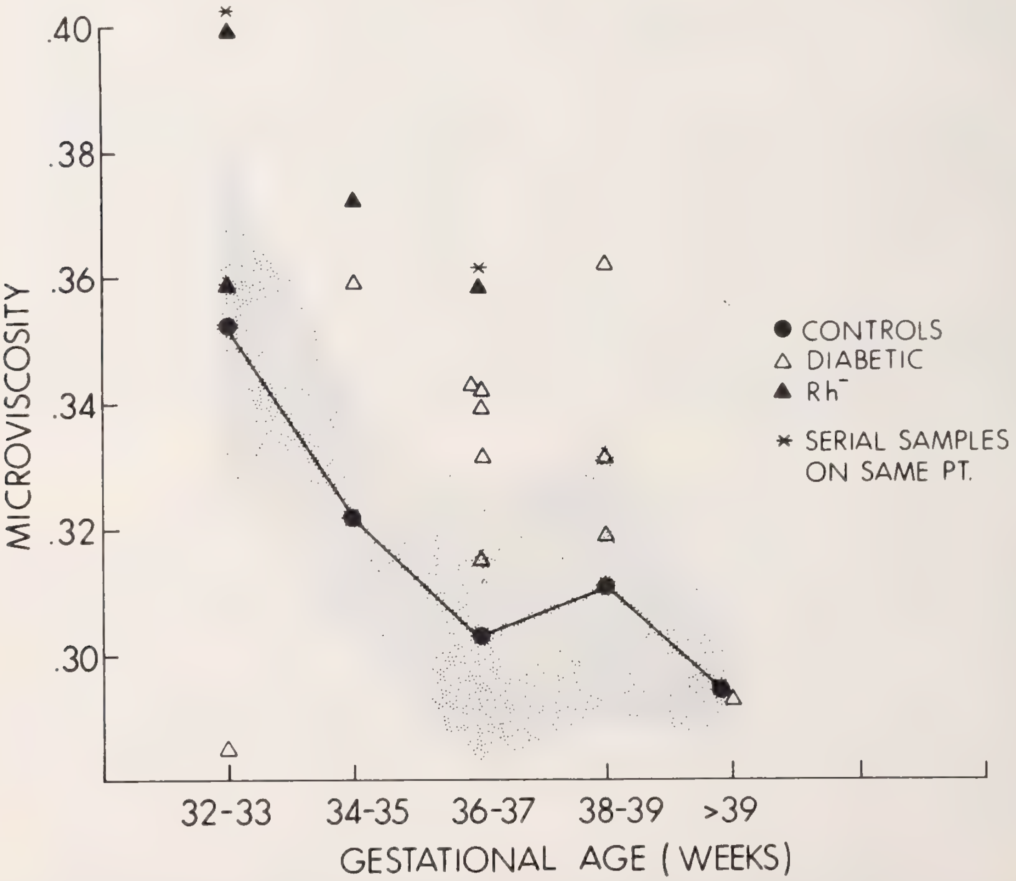

Fig. 1. Change in microviscosity measurements of amniotic fluid during last part of gestation. Solid line connecting (●) depicts mean value for controls, and shaded area ± 25D for this group. Individual values for diabetic (△) and Rh$^-$ (▲) patients are also shown.

TABLE 2
Predictive Value Analysis of FP-MV, L/S ratio, and PG, All Patients

	FP-MV		LS		PG	
	Positive >.31	Negative <.31	Positive <2.0	Negative >2.0	Positive absent	Negative present
RDS	10	0	3	6	5	3
no RDS	27	13	4	38	12	20
Sensitivity	100%		33%		62.5%	
Specificity	32.5%		90.48%		66.67%	
Efficiency	46%		80.39%		62.50%	
Predictive value	27.03%		42.86%		29.41%	

gestational age are shown in Figure 1. In normal pregnancies FP-MV of amniotic fluid declined in late gestation, a plateau occurring between 36 and 37 weeks. In comparison, diabetic and Rh incompatible pregnancies exhibited significantly higher FP-MV values than normals at all gestational ages studied.

We compared the predictive values of each of the three tests, FP-MV determination, L/S ratio, and PG availability, employing Bayes theorem (Tables 2, 3) for all pregnancies as well as those complicated by diabetes and Rh^- incompatibility. In this analysis, the sensitivity of a test is indicated by the number of positive (i.e. abnormal) values in the presence of disease; the specificity of the test is the number of negative (i.e. normal) values in the absence of disease. The predictive value of a test is obtained as the percentage of positive results in the true disease group (i.e. sensitivity) when the test is applied to the population containing both healthy and diseased subjects (15). The efficiency of a test is determined by the ratio of the number of correct readings (i.e. true positives and true negatives) compared to the total number sampled.

For our study, positive tests (i.e. indicating disease) were defined as an FP-MV value of >0.31, L/S ratio <2.0, and PG absent in amniotic fluid. For all patients, FP-MV values of >0.310 showed extremely high sensitivity for the detection of RDS; the specificity and efficiency of this test were lower, and the predictive value of this test was 27%. The sensitivity of L/S ratios for the detection of RDS was considerably lower than FP-MV; however, the specificity and predictive value of L/S ratios were greater. Use of PG as a means of screening for RDS showed a sensitivity of 62%, specificity of 67%, and predictive value of 29%, which was comparable to FP-MV.

In pregnancies complicated by diabetes or erythroblastosis, FP-MV determination had a sensitivity of 100%; however, the specificity was very low at 12.5%. Thus, the predictive value of this test was 41.7%. In contrast, use of L/S ratio <2.0 had a sensitivity of 0%, specificity of 100% and thus had negligible predictive value. When an L/S ratio of <3.5 was used, as has been suggested by some authors (2, 3), the sensitivity increased to 22% and the predictive value to 33%. In complicated pregnancies, PG determinations on am-

TABLE 3
Predictive Value Analyses of FP-MV, L/S Ratio, and PG for Pregnancies Complicated by Diabetes Mellitus or Rh-Incompatibility

	FP-MV		L/S		PG	
	Positive >.31	Negative <.31	Positive <2.0	Negative >2.0	Positive absent	Negative present
RDS	5	0	0	5	3	0
no RDS	7	1	0	8	0	5
Sensitivity	100%		0%		100%	
Specificity	12.5%		100%		100%	
Predictive value	41.67%		0%		100%	
Efficiency	46.1%		61.5%		100%	

niotic fluid to predict neonatal outcome were highly predictive.

In uncomplicated pregnancies, FP-MV values showed 100% sensitivity, yet the predictive value was only 18%. L/S ratio determination proved more highly specific for the prediction of neonatal outcome than either FP-MV or PG determinations.

Discussion

The purpose of this study was to compare the efficacy of three methods employed in fetal lung maturity assessment in predicting the likelihood of neonatal RDS in complicated pregnancies. The results of our study showed that fluorescence-polarization measurement of amniotic fluid was a more highly sensitive method for assessing fetal lung maturity than L/S ratio determination in pregnancies complicated by diabetes or erythroblastic disease. The sensitivity of this method was comparable to that of PG determinations of amniotic fluid, although the latter had a significantly greater predictive value in the outcome of complicated pregnancies.

FP-MV provides an assessment of surface-tension lowering properties of the lipid micelles found in amniotic fluid and is dependent upon sum of surface-active lowering properties of all of the phospholipids found in fetal lung secretions (9–11, 16). The major component of lung surfactant is disaturated PC, which comprises nearly 40% of total surfactant phospholipid (5); however, other forms of PC are also synthesized which have less surface-tension lowering capabilities. In addition, it has been reported that phosphatidylglycerol (PG) an acidic phosphatide making up only a minor portion of pulmonary phospholipids, has a profound effect in lowering surface tension (6, 8, 16).

Unlike previous investigators, we were unable to observe any correlation between L/S ratio and fluorescence polarization measurements (17, 18). In diabetic pregnancies in particular, the lack of correlation between these two methods for assessing lung maturity was striking. This may reflect reduction in the synthesis of DSPC in fetal offspring of diabetic pregnancies, despite normal PC (lecithin) synthesis (14, 18–21). We have recently shown, in an experimental animal model of diabetic pregnancy, a very highly significant correlation between fetal lung DSPC content and amniotic fluid FP-MV determinations (Neufeld, Corbo, Braunstein; unpublished observation). More importantly, FP-MV measurements appear to reflect the presence or absence of phosphatidylglycerol in amniotic fluid confirming previous observations (16). As Cunningham has shown, the presence of PG is a better indicator of lung maturity in diabetic pregnancy than L/S ratio (8).

In our study the predictive value of FP-MV in uncomplicated pregnancies differed from previous reports (11, 12). However, in complicated pregnancies it is evident that the predictive value of this test is much greater than the two other methods currently in use. From the results of this study, we believe that FP-MV measurements are highly sensitive in the prediction of RDS, and thus provide the single best preliminary test in the management of complicated pregnancies. For those situations where the FP-MV values is abnormal, further analysis using L/S ratio or phospholipid profile determination should be employed.

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Electrocardiographic Patterns of Normally Functioning Dual Chamber Pacemakers

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The term "physiologic pacemakers" generally refers to pulse generators that employ dual-chamber pacing primarily to maintain atrial and ventricular synchronous contraction (1). In 1974 the Inter-Society Commission for Heart Disease formulated a three-letter code to describe pacemaker functions (2). The first letter of the code designates the chamber(s) paced (A = atrium, V = ventricle, D = dual). The second letter refers to the chamber(s) sensed (A = atrium, V = ventricle, D = dual, 0 = none). The third letter describes the mode of response to sensed spontaneous events (I = inhibited, T = triggered, D = dual, 0 = none or asynchronous).

The purpose of this report is to describe the potential electrocardiographic manifestations of normally functioning dual-chamber pacemakers, mainly the VAT (ventricular-pacing, atrial-sensing, and atrial-triggered mode); VDD (ventricular-pacing, atrial- and ventricular-sensing, atrial-triggered, and ventricular-inhibited modes); DVI (atrial- and ventricular-pacing in sequence, ventricular-sensing, ventricular-inhibited mode); and DDD (atrial- and ventricular-pacing in sequence, atrial- and ventricular-sensing, atrial-inhibited and -triggered, and ventricular-inhibited mode).

During the past 4 or more years, an increasing number of physiologic pacemakers have been implanted for symptomatic sick sinus syndrome or significant atrioventricular block (3). Since then, numerous pacemaker electrocardiographic rhythms have emerged after implantation of dual-chamber pacers (4, 5). Most of these rhythms are straightforward, some are more complicated, and still others are not easily understandable. Although several atrial synchronized pacemaker arrhythmias have been previously described (6–8), the newer and more complex dual-chamber devices have generated a myriad of electrocardiographic rhythm disturbances which continue to challenge most physicians and manufacturers alike in the correct analyses of normal and abnormal pacemaker functions (9).

Definitions

Probably one of the major reasons for the difficulty in assessing pacemaker electrocardiograms (ECGs) is the limited availability of standardized terminology as it applies to pacemaker electrocardiography. The unrestricted use and abuse of various definitions have often confused the issues instead of establishing more acceptable and less debatable pacemaker-modified ECG interpretations (10). Even with the revised ICHD pacemaker codes (11) there are still inappropriate descriptions of these current ECG pacing patterns.

From knowledge that has accumulated with the use of the conventional single-chamber ventricular demand pacemakers, several definitions are hereby proposed which will be used throughout the discussion.

1. **P**—spontaneous atrial depolarization or P wave.
2. **R**—spontaneous ventricular depolarization or QRS complex.
3. S_A or **A**—artificial pacing stimulus or output

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delivered to the atrium and manifested on the ECG as a sharp monophasic spike.

4. S_V or V—artificial pacing stimulus or output delivered to the ventricle manifested on the ECG as a sharp monophasic spike.

5. **Pacing**—delivery of pacing stimulus or output to either atrium or ventricle or both which may or may not result in depolarization of the respective chamber(s).

6. **Capture**—depolarization of either atrium or ventricle or both upon delivery of the pacing stimulus or output.

7. **Automatic pacing interval**—the interval in milliseconds (msec) from one pacing stimulus (A or V) to the next or subsequent pacing stimulus (A or V); also referred to as free-running pacing interval or basic pacing rate expressed in pulses per minute (ppm) (Fig. 1).

8. **S_A-S_A or S_V-S_V interval**—the interval in milliseconds from one atrial or ventricular pacing output to the next or corresponding atrial or ventricular stimulus during automatic dual-chamber (DVI or DDD) pacing (Fig. 1).

9. **S_V-S_A (or V-A) interval**—the interval in milliseconds from the ventricular stimulus to the next or subsequent atrial stimulus during automatic dual-chamber (DVI or DDD) pacing (Fig. 1).

10. **S_A-S_V (or A-V) interval**—the interval in milliseconds from the atrial stimulus to the sequential ventricular stimulus during automatic dual-chamber (DVI or DDD) pacing when sinus rate is below basic pacing rate (Fig. 1).

11. **P-S_V (or P-V) interval**—the interval in milliseconds from the onset of a sensed spontaneous P wave to the triggered ventricular stimulus during VAT, VDD, or DDD but not DVI mode of pacing when the sinus rate is above the basic or backup pacing rate. This interval may or may not be exactly equal to the programmed A-V interval.

12. **A-V delay**—originally used to describe the electronic time lag between a sensed spontaneous atrial event and the triggered ventricular pacing stimulus in the VAT pulse generator (12). At present A-V delay refers to either S_A-S_V interval

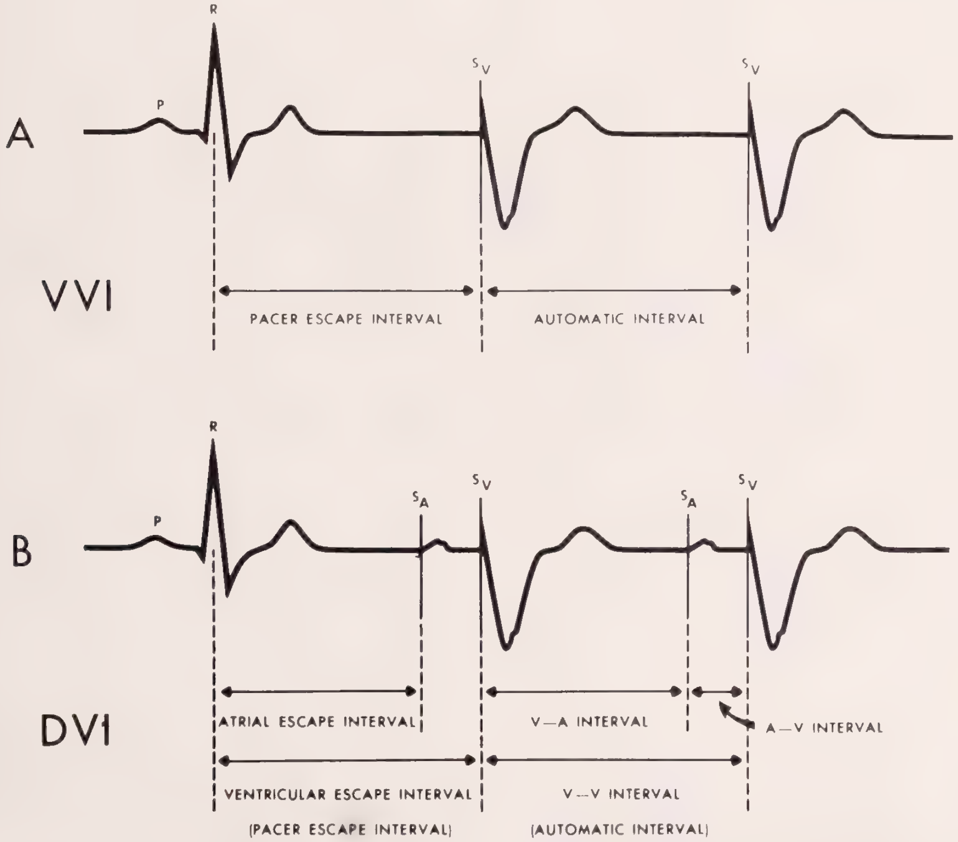

Fig. 1. Schematic diagram comparing various timing intervals between single chamber pacemaker (VVI) and dual chamber pacemaker (DVI). Panel A shows spontaneous P-QRS complex followed by ventricular pacing at end of pacemaker escape interval. Second and third beats are ventricular paced beats. Pacemaker escape interval is similar but not necessarily equal to automatic pacing interval, depending upon where sensing of spontaneous QRS occurs on surface ECG. Panel B shows spontaneous P-QRS complex followed by atrial and ventricular pacing in sequence. Second and third beats are both pacing induced. P-wave has slightly different configuration followed by wide QRS complex in these two beats to indicate atrial and ventricular capture respectively. P, P-wave; R, QRS; A or S_A, atrial pacing stimulus; V or S_V, ventricular pacing stimulus.

or P-S_V interval. However, S_A-S_V interval will be used when referring to the measurement from an atrial pacing stimulus to the sequential ventricular pacing output, whereas P-S_V interval will be used specifically when referring to atrial synchronized ventricular pacing (VAT, VDD, or DDD).

13. **Pacemaker escape interval**—the interval in milliseconds from the onset of a sensed or paced atrial or ventricular event to the delivery of a pacing stimulus (A or V). This may be further subdivided as follows: (a) QRS-to-A interval—the interval in milliseconds from the onset of a sensed spontaneous ventricular event (QRS) to the delivery of the subsequent atrial pacing stimulus which may or may not be equal to the S_V-S_A interval. (b) QRS-to-V interval—the interval in milliseconds from the onset of a sensed spontaneous ventricular event (QRS) to the delivery of the subsequent ventricular pacing stimulus, which may or may not be equal to the S_V-S_V interval (Fig. 1).

14. **Fusion beat**—the ECG pattern resulting from simultaneous atrial or ventricular depolarization from two foci, one spontaneous and the other pacer-induced, i.e., atrial or ventricular fusion beats, respectively (13).

15. **Pseudofusion beat**—the electrocardiographic superimposition of an ineffective atrial and/or ventricular pacing stimulus on a spontaneous P wave and/or QRS complex originating from a single focus, i.e., atrial pseudofusion and/or ventricular pseudofusion beats, respectively (13).

16. **Maximum rate limit or upper rate limit**—also called maximum tracking rate when referring to the fastest ventricular pacing rate achievable on a 1:1 basis during atrial synchronized ventricular pacing (VAT, VDD, or DDD).

17. **Minimum rate limit or lower rate limit**—also called backup or basic pacing rate when there are no detectable spontaneous atrial events during VAT, VDD, or DDD mode of pacing.

18. **Tracking**—atrial synchronized ventricular pacing in the VAT, VDD, or DDD pulse generators.

Normal VAT Electrocardiographic Patterns

Although it is not now used, the VAT pulse generator represents the first model of a physiologic pacemaker that maintains atrioventricular synchrony (12). Sensing of a spontaneous atrial event through the atrial electrode initiates an electronic A-V delay at the end of which triggered ventricular pacing occurs. Maximum ventricular pacing is limited by a nonprogrammable atrial pacemaker refractory period. Various degrees of 2:1, 3:1, or 4:1 pacer block may be seen during episodes of supraventricular tachycardias when the atrial rate exceeds the maximum rate limit. There is no sensing capability in the ventricular electrode. Hence, during periods of sinus bradycardia or sinus arrest, fixed rate or asynchronous ventricular (V00) pacing occurs.

Depending on the status of atrioventricular conduction, several ECG patterns may be seen: (a) atrial or P-synchronized ventricular capture; (b) atrial or P-synchronized ventricular fusion; (c) atrial or P-synchronized ventricular pseudofusion; (d) asynchronous ventricular pacing (atrial rate less than back-up rate).

VAT pulse generators or modes of pacing are no longer utilized because of the competition with spontaneous QRS complexes and the potential for inducing serious ventricular tachyarrhythmias (14).

Normal VDD Electrocardiographic Patterns

Similar to the VAT unit, a VDD pulse generator or mode of pacing detects spontaneous atrial events, initiates an electronic A-V delay, and then paces the ventricle at the completion of the P-S_V interval. In contrast, however, the addition of a sensing filter in the ventricular lead allows inhibition of ventricular pacing if a spontaneous QRS is detected before the end of the P-S_V interval (15). Furthermore, during periods of sinus bradycardia or sinus arrest, the VDD unit automatically switches to ventricular demand (VVI) pacing at the backup rate (Fig. 2). The various ECG patterns are therefore those of atrial or P-synchronized ventricular pacing with ventricular capture, fusion, or pseudofusion as well as ventricular capture, fusion, or pseudofusion of a QRS complex during standby VVI pacing. Ventricular pacing is also inhibited after a sensed atrial event when the P-R interval is shorter than the programmed P-S_V interval. Junctional or ventricular premature beats likewise inhibit ventricular stimulation with or without a preceding P wave.

Normal VDD electrocardiographic patterns are as follows: (a) atrial or P-synchronized ventricular capture; (b) atrial or P-synchronized ventricular fusion; (c) atrial or P-synchronized ventricular pseudofusion; (d) atrial or P-synchronized ventricular inhibited ($P - R < P - V$ interval); (e) ventricular demand pacing with capture, fusion, or pseudofusion (atrial rate less than backup rate); (f) ventricular inhibited with or without a preceding P-wave during junctional or ventricular premature beats.

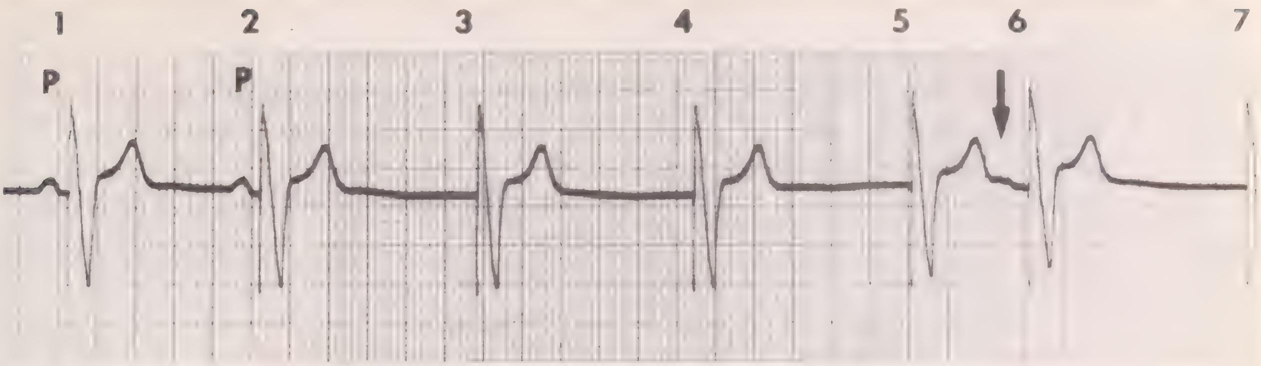

Fig. 2. Lead 2 rhythm strip from patient with VDD pulse generator programmed in VDD mode with maximum rate limit of 100 ppm and minimum or backup rate of 55/min. Beats 1 and 2 demonstrate atrial or P-synchronized ventricular pacing at rate of 60/min with P-V interval of 160 msec. This is probably followed by episode of sinus bradycardia, hence the third, fourth, and fifth complexes demonstrate ventricular paced beats at 55/min with no discernible preceding P-waves. Sixth complex shows atrial premature beat (arrow) which occurs after atrial refractory period and is therefore sensed by pacemaker. It initiates P-V interval at end of which ventricular paced beat occurs approximately 600 msec from preceding paced event, equivalent of 100 ppm or maximum rate limit. This is again followed by absence of detectable atrial activity; hence, another ventricular paced beat (7) at approximately 55 beats/min is demonstrated.

A programmable maximum rate limit is also available in the VDD pulse generator (16). Some dual-chamber units when programmed in the VDD mode of pacing may manifest progressive lengthening of the P-S_V interval during periods of supraventricular tachycardias until a blocked P wave falls within the pacemaker atrial refractory period. This ECG pattern has been described as "pacemaker Wenckebach-like behavior," but unlike true Wenckebach, the paced QRS intervals are constant. Other units may manifest as 2:1, 3:1, or 4:1 block on the ECG depending on the spontaneous atrial rate, the duration of a pacemaker total atrial refractory period, and the maximum rate limit period (17).

Normal DVI Electrocardiographic Patterns

Atrioventricular sequential demand pulse generator or DVI mode of pacing refers to stimulation of both atrium and ventricle sequentially with sensing or inhibition of pacing occurring through the ventricular lead only (18). The atrial-pacing stimuli may therefore appear on the ECG regardless of whether spontaneous P waves are present or not since there is no sensing capability in the atrial electrode.

Two types of DVI pacemakers are presently available: the noncommitted and the committed units. The basic difference between these two units depends on when the pacemaker ventricular refractory period is initiated. In the noncommitted type, the pacemaker refractory period starts from the ventricular stimulus or upon detection of a spontaneous QRS complex. In contrast, the refractory period of the committed unit begins from the atrial stimulus or sensing of spontaneous QRS complex. This refractory period following an atrial stimulus extends for about 332 msec and includes the ventricular spike which is obligatorily released 150–155 msec from the atrial stimulus. Sensing of spontaneous ventricular events during the pacemaker escape interval is also called the alert period. This sensing period ends upon delivery of the atrial-pacing stimulus in the committed unit. In the noncommitted type, the alert period is relatively longer and continues through the S_A-S_V interval until a paced or sensed ventricular event occurs (18).

Although paired atrial and ventricular pacing occurs with equal frequency in both types, atrial spikes alone may be seen at times in the noncommitted system. These atrial stimuli may appear on the P-R segment or just before the onset of a spontaneous QRS complex. Atrial pacing may also manifest when the intrinsic P-R interval is shorter than the programmed S_A-S_V interval. Depending on the sinus rate and abnormalities in atrioventricular conduction, atrial pacing may also occur with ventricular capture, fusion, or pseudofusion of the QRS complex. In addition, since the atrial lead does not sense spontaneous P waves, atrial fusion, pseudofusion, or noncapture of the atrium after a P wave may appear as a normal ECG pattern and does not necessarily imply pacemaker malfunction (Fig. 3).

Furthermore, in the DVI committed system, atrial noncapture after spontaneous P waves may normally occur in combination with ventricular noncapture (Fig. 4). These peculiar but otherwise normal ECG pacing patterns probably represent the most frequently misinterpreted DVI paced rhythm. These patterns have been described in various forms including "pseudopseudofusion," "double pseudofusion," and "sandwiched" beats (19). The majority of these pacemaker rhythms actually represent superimposition of ineffective atrial and ventricular stimuli on the spontaneous P-QRS complexes.

Thus, in order to avoid further confusion, a much simpler description of these normal DVI committed ECG patterns is proposed as follows: (a) atrial spike on the P wave with ventricular spike on the P-R segment or onset of spontaneous QRS; (b) atrial spike on the P-R segment with ventricular spike on the spontaneous QRS; (c) atrial spike at the onset of spontaneous QRS with ventricular spike at the end of the QRS; and (d) atrial spike near the end of the spontaneous QRS and ventricular spike on the S-T segment or T wave. The fourth pattern may normally occur during late sensing of wide QRS complexes such as in bundle branch blocks, intraventricular conduction defects, or ventricular extrasystoles (20, 21).

Normally, therefore, various combinations of pacemaker ECG patterns may be seen with the DVI pulse generators:

1. Atrial capture and ventricular capture.
2. Atrial capture and ventricular fusion.
3. Atrial capture and ventricular pseudofusion.
4. Atrial capture and ventricular inhibited (noncommitted unit).
5. Atrial fusion and ventricular capture.
6. Atrial fusion and ventricular fusion.
7. Atrial fusion and ventricular pseudofusion.
8. Atrial fusion and ventricular inhibited (noncommitted unit).
9. Atrial pseudofusion and ventricular capture.
10. Atrial pseudofusion and ventricular fusion.
11. Atrial pseudofusion and ventricular pseudofusion.
12. Atrial pseudofusion and ventricular inhibited (noncommitted unit).
13. Atrial non-capture and ventricular capture.
14. Atrial non-capture and ventricular fusion.
15. Atrial non-capture and ventricular pseudofusion.
16. Atrial non-capture and ventricular inhibited (noncommitted unit).
17. Atrial non-capture and ventricular non-capture (committed unit):
    (a) atrial spike on P wave and ventricular spike on P-R or onset of QRS;
    (b) atrial spike on P-R and ventricular spike on QRS;
    (c) atrial spike at onset of QRS and ventricular spike at end of QRS;
    (d) atrial spike at end of QRS and ventricular spike at ST segment or T wave.
18. Atrial and ventricular inhibited.

Normal DDD Electrocardiographic Patterns

Dual-chamber or atrioventricular universal DDD pulse generators are complex devices that are capable of sensing and pacing in both atrium and ventricle. Detection of spontaneous atrial events initiates an electronic A-V delay and triggers ventricular pacing unless a spontaneous

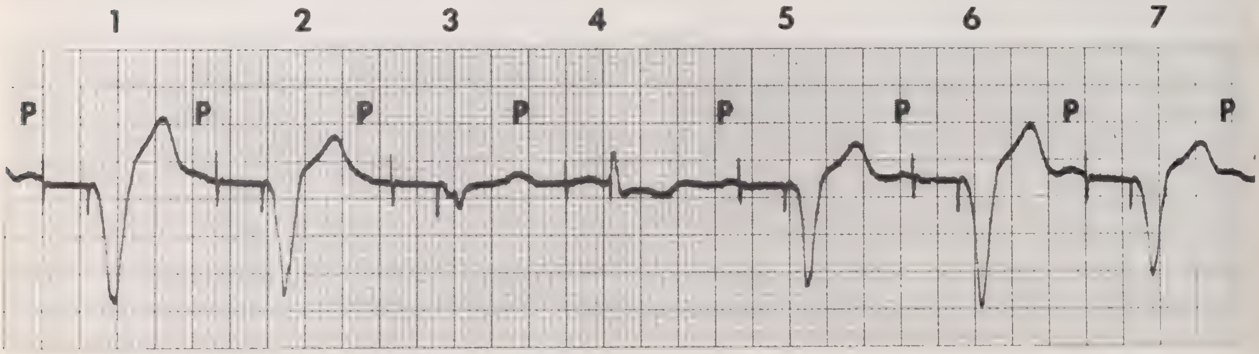

Fig. 3. Lead 2 rhythm strip obtained from patient with noncommitted DVI Medtronic pulse generator programmed at rate of 63/min with A-V interval of 250 msec. The first three beats demonstrate absence of atrial capture because stimuli are delivered during refractory period of spontaneous preceding P-waves. First two QRS complexes, however, clearly demonstrate ventricular capture, whereas third QRS demonstrates ventricular fusion. Fourth beat illustrates atrial capture with ventricular pseudofusion. Ventricular spike occurs immediately after inscription of narrow QRS complex. Fifth, sixth, and seventh beats are identical to the first two beats, demonstrating atrial pseudofusion or noncapture with ventricular capture.

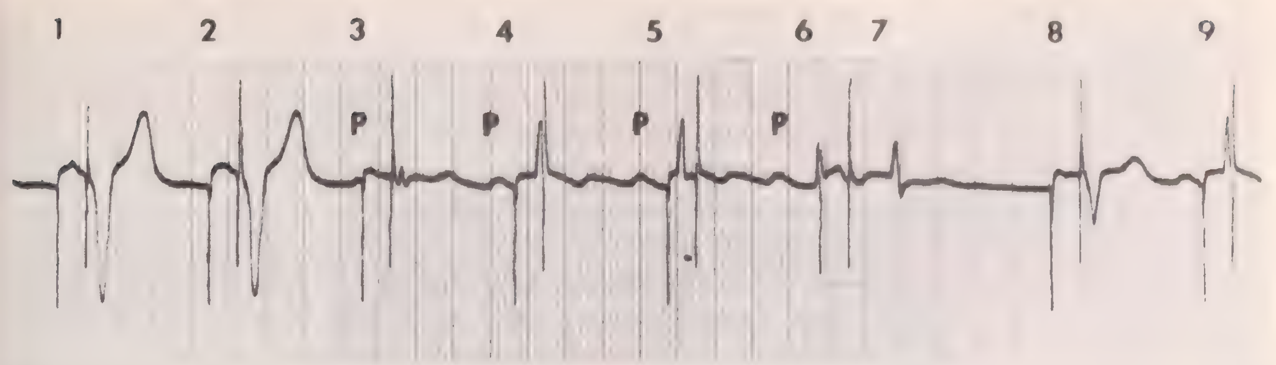

Fig. 4. Lead 2 rhythm strip obtained from patient with committed DVI Intermedics Cyberlith IV programmed at rate of 72/min. First two complexes show A-V pacing with atrial and ventricular capture. On third beat, atrial spike is emitted immediately after inscription of spontaneous P-wave. Ventricular spike-QRS complex demonstrates true fusion beat. Subsequent fourth, fifth, and sixth beats demonstrate superimposition of ineffective but normal A and V spikes on spontaneous P-QRS complexes with atrial spike on P-wave and ventricular spike on QRS, atrial spike on P-R segment and ventricular spike on ST segment, and atrial spike at onset of QRS and ventricular spike near T wave, respectively. Seventh beat is premature supraventricular beat which inhibits A-V pacing. This is followed by pacemaker escape interval at end of which A and V spikes occur. Pacemaker escape interval is approximately equal to A-V interval plus V-A interval (or A-A or V-V interval), a characteristic feature of Intermedics DVI committed pulse generator. Eighth ventricular QRS complex is wide but not exactly identical to first two beats and may therefore represent fusion. Ninth complex again demonstrates superimposition of atrial and ventricular spikes on spontaneous P-QRS.

QRS complex is sensed prior to the completion of the P-S_V interval. Unlike the VAT or VDD mode of pacing, atrial pacing may occur at the completion of the S_V-S_A interval period during sinus bradycardia or sinus arrest (Fig. 5). This type of pacemaker therefore functions as both a VDD and a DVI unit depending on the sinus rate and the status of atrioventricular conduction. The various combinations of normal DDD ECG patterns are therefore similar to the previously described VDD and noncommitted DVI units:

1. Atrial or P-synchronized ventricular capture.
2. Atrial or P-synchronized ventricular fusion.
3. Atrial or P-synchronized ventricular pseudofusion.
4. Atrial or P-synchronized ventricular inhibited.
5. Atrial capture and ventricular capture.
6. Atrial capture and ventricular fusion.
7. Atrial capture and ventricular pseudofusion.
8. Atrial capture and ventricular inhibited.
9. Atrial fusion and ventricular capture.
10. Atrial fusion and ventricular fusion.
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12. Atrial fusion and ventricular inhibited.
13. Atrial pseudofusion and ventricular capture.
14. Atrial pseudofusion and ventricular fusion.

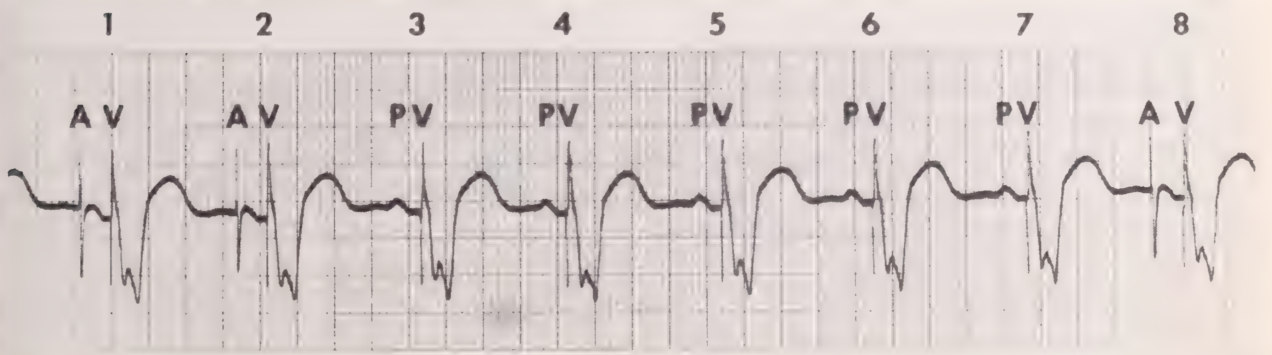

Fig. 5. Lead 2 rhythm strip obtained from a patient with a DDD pulse generator programmed in DDD mode at lower rate 70/min, A-V interval 160 msec and upper rate limit of 100 ppm. First two beats demonstrate A-V pacing with atrial and ventricular capture. Subsequent third to seventh beats are atrial or P-synchronized ventricular pacing with P-V interval of approximately 160 msec, identical to programmed A-V interval. Eighth beat again shows A-V pacing.

15. Atrial pseudofusion and ventricular pseudofusion.
16. Atrial pseudofusion and ventricular inhibited.
17. Atrial and ventricular inhibited (or similar to 4).
18. Same as VDD unit when on VDD mode.
19. Same as DVI noncommitted unit when on DVI mode.

Other DDD pacing patterns, especially in response to spontaneous atrial or ventricular extrasystoles, have been described elsewhere (22, 23).

Summary

From the foregoing discussion, it becomes apparent that multiple combinations of pacemaker-modified ECG rhythm disturbances are possible with the dual-chamber pulse generators. A thorough knowledge of their basic functional characteristics is essential for every physician involved in dual-chamber pacing. The difficult task of identifying the normal from the truly abnormal pacemaker function as manifested on the ECG has been inevitably placed on the interpreter. Although the challenge grows stronger as the newer pacemakers become more complex, the physician's responsibilities remain unchanged, namely, (a) to achieve correct and meaningful evaluation of dual-chamber pacer-modified ECGs, (b) to assure appropriate patient care, and (c) to avoid unnecessary pacemaker replacement.

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Factors Predisposing to Intraoperative Myocardial Infarction During Coronary Artery Bypass Surgery

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Abstract

Eighteen consecutive patients (group I) with Q-wave (18 patients) and enzymatic (16 patients) evidence of intraoperative myocardial infarction were compared to 42 patients without intraoperative myocardial infarction (group II) operated on during the same time period. Patients were compared with respect to age, sex, presence of hypertension, unstable angina, preoperative use of beta blockers, preoperative ejection fraction, number of bypassed vessels, and extracorporeal circulation time. In addition, severity of stenosis and presence of collaterals in the 18 infarct-related arteries (group IA vessels) was compared to the 32 noninfarct-related arteries in group I patients (group IB vessels) and to the 105 bypassed vessels in group II patients (group II vessels). Group I patients had significantly ($p < 0.02$) longer pump time (140.3 ± 51 min) than group II patients (101.9 ± 30 min). Group IA vessels were more severely stenotic than group II vessels ($p < 0.05$). Group IA vessels were not significantly more stenotic than group IB vessels, but collaterals were present significantly ($p < 0.02$) more often to group IB vessels with greater than 95% stenosis than to group IA vessels with a similar degree of stenosis. Intraoperative myocardial infarction during bypass surgery is more common distal to very severely stenotic coronary arteries without collaterals and related to prolonged duration of extracorporeal circulation.

Acute myocardial infarction is a known complication of patients undergoing coronary artery bypass surgery. The frequency with which this occurs has been reported to be from 2% to 40%, the incidence decreasing in recent reports; however, intraoperative myocardial infarction continues to occur, probably having an adverse effect on prognosis (1–8). The fact that myocardial infarction may occur during surgery despite a patent graft to the area of infarction (9) has led to interest in the causes of intraoperative myocardial infarction. The present study was designed to examine baseline and intraoperative variables as possible predisposing factors influencing the occurrence of intraoperative myocardial infarction.

Methods

Patient Population. The study population consisted of 18 consecutive patients who had an intraoperative myocardial infarction during coronary artery bypass surgery; there were 16 males and two females aged 36–76 years (mean 57.2) (group I). A control group of 42 patients was randomly selected from computer printouts listing patients operated on during the same period, and who had no myocardial infarction (group II). There were 38 males and four females aged 34–75 years (mean 56.2). No attempt was made to determine the incidence of myocardial infarction in patients undergoing coronary artery bypass surgery at our institution.

Patients excluded were those undergoing re-

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operation for coronary disease, those whose bypass surgery included associated procedures such as ventricular aneurysmectomy or valvular replacement, those with coronary artery endarterectomy, and those with intraoperative infarction in an area of myocardium subtended by a nonbypassed coronary artery. Patients with previous myocardial infarction were not excluded.

Data to Be Evaluated. Patients were analyzed with regard to age, sex, hypertension, diabetes mellitus, preoperative beta-blocking therapy, and unstable angina pectoris as defined by the National Cooperative Study Group (10). Myocardial infarction was diagnosed when new Q waves (greater than 1.0 mm in depth and 0.03 sec in width) and abnormal enzymes were present and persistent. The preoperative electrocardiogram was compared with the first electrocardiogram taken after the operation. A loss of R waves in the right precordial leads was also considered diagnostic of myocardial necrosis in the presence of abnormal enzyme elevations. All electrocardiograms were read by two cardiologists. When disagreement existed, a third opinion was obtained and consensus was reached. The enzymes were considered suggestive of intraoperative myocardial infarction if the postoperative creatine kinase MB fraction was greater than 10 IU as determined by column chromatography. In the absence of creatine kinase MB determination, an elevation of serum glutamic oxalacetic transaminase to greater than twice normal value in association with an elevation of total creatine kinase to greater than four times normal was considered suggestive of infarction (11).

Myocardial infarction was diagnosed by electrocardiographic and enzyme criteria in 16 of 18 group I patients and by electrocardiographic criteria alone in 2 of 18, as timely enzymatic determinations were not available. Extracorporeal circulation time was available for 15 of 18 group I patients and 39 of 42 group II patients. Aortic cross-clamp time was not available.

Coronary cinearteriography and left ventriculography were performed prior to operation by either the brachial or femoral approach using standard techniques. Ejection fraction was calculated from right anterior oblique monoplanar left ventricular angiograms using standard techniques (12). Ejection fraction was calculated in all but two patients in each group because of lack of a suitable sinus beat. Coronary angiograms were analyzed prior to surgery by one or two experienced angiographers, who were of necessity blinded to the results of surgery. Postoperatively, a different experienced angiographer analyzed the angiograms blinded to the preoperative interpretation but not blinded to the results of surgery. If disagreement existed, another totally blinded opinion was obtained and a consensus was reached.

Coronary arteries were analyzed in multiple views, and stenoses were characterized by percentage diameter narrowing and then grouped as moderate (<80%), severe (80%–94%), or very severe (95%–100%). Collaterals were considered to be present if they were visible angiographically or if a totally occluded vessel filled in retrograde fashion beyond the area of total obstruction. No attempt was made to quantify collaterals.

Because of marked differences in the degree of filling of a coronary artery distal to an obstruction, the distal luminal caliber was not quantitated angiographically for the purposes of this study.

Infarct-Related Vessel. The infarct-related artery was determined by correlation of the electrocardiographic zone of infarction and the coronary anatomy of each patient. In most cases, anteroseptal myocardial infarction was related to the area perfused by the left anterior descending, inferior myocardial infarction to the right coronary artery, and inferolateral or true posterior myocardial infarction to the circumflex. Three vessel groups were defined. Group IA vessels are the 18 grafted infarct-related vessels in group I patients. Group IB vessels are the 32 bypassed vessels in group I patients that were not infarct-related. Group II vessels are the 105 bypassed vessels in group II patients.

Operative Technique. Standard cardiopulmonary bypass techniques were employed. Extracorporeal circulation time (pump time) was measured from the time of onset of partial bypass to time completely off bypass. In addition to standard cold potassium cardioplegic technique, cardioplegic solution was infused selectively into some arteries with severe obstruction. This was done through the arteriotomy that would later accept the graft and until the temperature of the subtended myocardium dropped to the same temperature as the rest of the heart (usually 5–8°C) (13). This procedure usually required an additional 3–5 min. Data on the percentage of patients in each group who received distal perfusion were not available.

Statistical Analysis. Chi-square tests of significance and Student's *t* test were used to test hypotheses. Statistical significance is reported with corresponding *p* values. Observed probability levels for all tests were recorded to indicate trends.

Results

The baseline clinical data in group I and II patients are shown in the Table. None of the observed characteristics, including age, sex, anginal status, presence of hypertension or diabetes, preoperative use of beta blockers, preoperative ejection fraction, and number and location of diseased and bypassed vessels, revealed any significant difference between groups.

Severity of Stenosis. The distribution of severity of stenosis in vessel groups IA, IB, and II is shown in Figure 1. None of group IA vessels had stenosis of less than 80%, 4 of 18 (22%) had stenosis of 80%–94%, and 14 of 18 (78%) had stenosis greater than or equal to 95%. In comparison, 22 of 105 (21%) group II vessels had less than 80% stenosis, 30 of 105 (29%) had stenosis of 80%–94%, and 53 of 105 (50%) had stenosis of 95% or more. These data indicate that infarct-related arteries (group IA) were more severely stenotic than noninfarct-related arteries (group II) ($p < 0.05$). There is no significant difference between groups IB and II. Comparing group IA vessels to group IB plus group II vessels (all non-infarct-related vessels in both patient groups), there was a trend to more severe stenosis in the infarct-related vessels (group IA) ($p = 0.08$).

Presence of Collaterals. The presence of collaterals to vessels with 95% or more stenosis in each vessel group is shown in Figure 2. Significantly fewer vessels were collateralized in group IA than in group IB (36% versus 76%, $p < 0.02$). There were also fewer collateralized vessels in group IA than in group II (36% versus 59%), although this difference did not achieve statistical significance ($p = 0.15$). Among the three vessel groups, vessels with less than 95% stenosis did not differ significantly in percentage of collaterals.

Pump Time. Patients who suffered intraoperative infarcts had a significantly longer cardiopulmonary bypass time (140 ± 51 min) than those without infarction (101 ± 30 min) ($p < 0.02$) (Fig. 3). The number of grafts in group I and group II patients was not significantly different and could not account for the difference in pump time.

Discussion

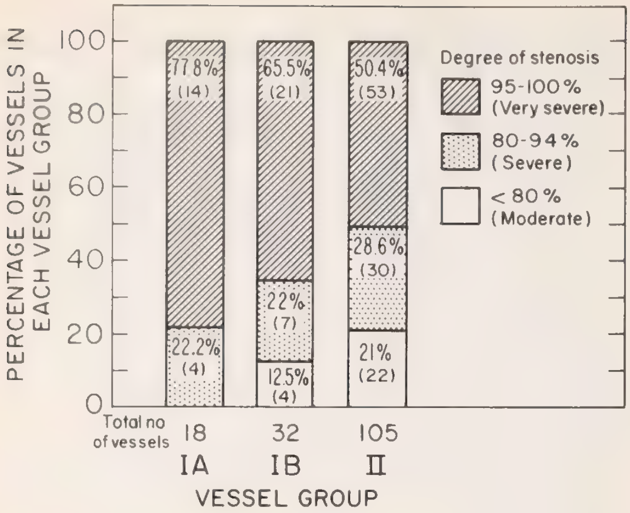
The preoperative and intraoperative parameters that predispose to myocardial infarction during coronary artery bypass surgery are not clearly defined. Some centers have shown a correlation between the decrease in frequency of intraoperative infarction and the surgical experience of the operative team (4, 14–18). The reasons most frequently cited to account for the decreased incidence of infarction have included improved surgical technique, shorter pump time

TABLE

Clinical and Angiographic Characteristics of Study and Control Groups

	Group I (IOMI)	Group II (Non-IOMI)
Number	18	42
Mean age, years (range)	57.2 ± 10.1 (36–76)	56.2 ± 9.5 (34–75)
Sex	16 male 2 female	38 male 4 female
Hypertension	6 (33%)	15 (36%)
Diabetes mellitus	3 (17%)	6 (14%)
Stable angina	10 (56%)	25 (60%)
Unstable angina	7 (39%)	16 (38%)
No angina	1 (5%)	1 (2%)
Mean preoperative ejection fraction (number of patients)	69.9 ± 18.9% (n = 16)	65.9 ± 16.4% (n = 39)
Beta-blocking agents	14 (78%)	35 (83%)
One-vessel disease	2 (11%)	4 (10%)
Two-vessel disease	3 (17%)	12 (29%)
Three-vessel disease	13 (72%)	26 (62%)
Left main (>50% stenosis)	2 (11%)	5 (12%)
LAD number bypassed	22 (44%)	47 (25.7%)
CFX number bypassed	13 (26%)	31 (29.5%)
RCA number bypassed	15 (30%)	27 (44.8%)
Total number of bypassed vessels	50 (100%)	105 (100%)
Average number of bypassed vessels	2.78	2.50

IOMI, intraoperative myocardial infarction; LAD, left anterior descending; CFX, circumflex; RCA, right coronary artery.



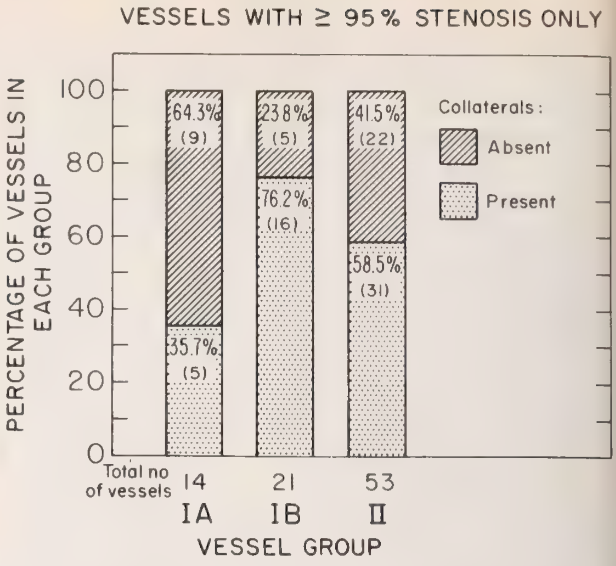


Fig. 1. Left Percentage of vessels in each vessel group by degree of stenosis.

Fig. 2. Right Percentage of vessels with greater than 95% stenosis in each vessel group with and without collaterals.

(3) and aortic cross-clamp time (19, 20), and improved methods of myocardial preservation (14, 15, 17, 21). However, all the determinants of intraoperative infarction have not been positively identified.

Mechanism of Intraoperative Infarction. The findings of our study suggest possible mechanisms for intraoperative infarction. Although we did not do routine postoperative angiography in our patients, previous studies have not found graft patency to influence the occurrence of intraoperative infarction (19, 22, 23). Bulkley and Hutchins (9) reported on postmortem examinations performed within 1 month of bypass surgery in 58 patients. Twenty-two of fifty-eight had regional transmural necrosis. Of these 22, 15 were in the distribution of a widely patent graft, four were in the distribution of an occluded graft, and three were in a nongrafted distribution. Two distinct types of necrosis were present. Contraction band necrosis was present in the myocardium supplied by widely patent grafts and by nongrafted arteries, and coagulation necrosis was present in the distribution of occluded grafts. Contraction band necrosis has been shown to occur after coronary occlusion followed by reperfusion, and coagulation necrosis after permanent occlusion (24).

Intraoperative myocardial infarction probably occurs in areas of myocardium suffering ischemic damage prior to restoration of blood flow. Reperfusion to an ischemic area of myocardium through a patent graft may have one of several effects. Reestablishment of oxygen delivery may cause reversal of ischemic injury. Alternatively, ischemic areas destined to progress to irreversible necrosis may be unmasked by reperfusion and develop the appearance of contraction band necrosis. Finally, it is possible that areas with potentially reversible injury may actually suffer irreversible damage because of abrupt reestablishment of blood flow through the patent graft.

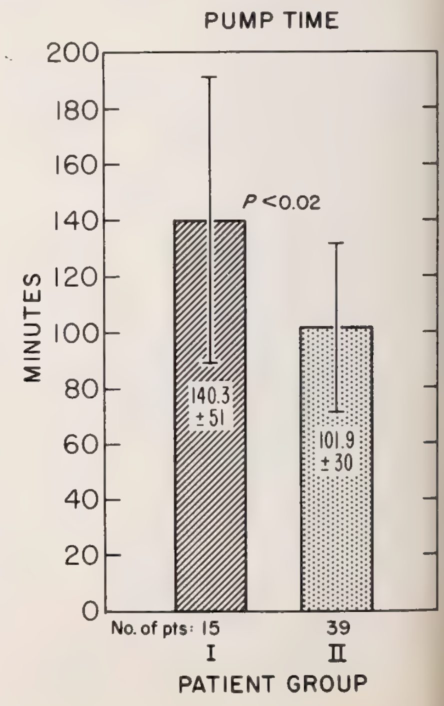


Fig. 3. Duration of extracorporeal circulation in patients with (group I) and without (group II) intraoperative infarction.

Severity of Stenosis. In our study we found that intraoperative myocardial infarction occurred exclusively in myocardium supplied by arteries with greater than 80% stenosis, and the vast majority (14/18) occurred distal to stenoses greater than 95%. The greater degree of stenosis in patients with intraoperative infarction was statistically significant. This is in agreement with Du Cailar et al. (20) and Brindis et al. (23), who found a higher incidence of myocardial necrosis perioperatively in patients with more severe preoperative coronary stenosis.

Areas of myocardium supplied by severely stenotic vessels are especially vulnerable to ischemic damage. This may be the result of several factors. A decrease in coronary perfusion pressure caused by transient hypotension would result in a greater decrease in flow through a more severe stenosis than through a lesser obstruction. The frequent occurrence of unrecognized episodes of transient hemodynamic compromise during induction of anesthesia has been described (25). The protection against ischemic injury afforded by cold cardioplegia may be lessened in areas distal to a severe coronary stenosis because of inadequate delivery of cardioplegic solution through a tight lesion (13, 17).

Protective Effect of Collaterals. Collaterals were significantly more frequently present to noninfarct-related arteries with greater than 95% stenosis than to infarct-related vessels with a similar degree of stenosis. Collateral blood flow may be sufficient in some instances to adequately augment blood supply or deliver cardioplegic solution to prevent ischemic damage during surgery. The protection of collaterals is variable as transient decreases in coronary perfusion pressure may cause a decrease in flow through narrow collateral channels similar to the decrease in flow through a severely stenotic vessel. Our finding that collaterals may protect against intraoperative infarction is corroborative of a similar finding by Namay et al. (8).

Duration of Extracorporeal Circulation. The duration of extracorporeal circulation has been related to an increased incidence of intraoperative infarction (3, 20, 26, 27). However, some authors have found no relationship (5, 8, 28, 29). In our study pump time was significantly longer in patients with intraoperative infarction than in those without. This difference in pump time was not related to an increased number of grafts in patients with intraoperative infarction. Prolonged pump time may predispose myocardial tissue to ischemic damage prior to reperfusion.

Influence of Drugs. Pharmacologic interventions have been suggested as a means of improving myocardial protection. The calcium-channel-blocking agents verapamil (30), nifedipine (31), and diltiazem (32) may be useful in limiting ischemic injury during cardiopulmonary bypass or damage occurring during reperfusion. The effect may be due to more effective cardioplegia or, possibly, decreased calcium influx after reperfusion. Similarly, beta-blocking agents have been shown to inhibit myocardial necrosis after temporary coronary occlusion (33). This may relate to blocking the adverse effects of catecholamines. Beta blockers may be useful in conjunction with cold cardioplegia (21). We found no difference in the preoperative use of beta blockers between groups I and II, although the degree of intraoperative beta blockade was not quantitated. Because very few of our patients were taking calcium-channel-blocking agents, the effect of these drugs was not analyzed in our study.

Limitations of the Study

Diagnosis of Intraoperative Infarction. The present study has certain limitations. We used strict criteria for the diagnosis of myocardial infarction and may have overlooked small or nontransmural areas of intraoperative necrosis. Enzymatic and scintigraphic methods have shown evidence of myocardial necrosis in the absence of Q waves (34–36). Because the criteria for diagnosis of intraoperative myocardial infarction were the same in the study group and in the control group, our conclusions should not be altered by this limitation.

Quantification of Coronary Stenosis. Autopsy studies have suggested that angiographic determination of coronary artery stenosis may underestimate the severity of such stenosis (37, 38). Errors in angiographic analysis should be randomly scattered throughout group I and group II and should not significantly affect our conclusions.

Graft Patency. The unavailability of postoperative angiograms in our patients does not permit assessment of the role of graft patency as an etiologic factor for intraoperative infarction. The lack of these data, however, does not invalidate our other conclusions concerning the role of degree of stenosis, presence of collaterals, and duration of extracorporeal circulation.

Distal Cardioplegia. Since most but not all severely stenotic vessels had additional cardioplegic solution instilled distally, it was not possible to evaluate the effectiveness of this technique.

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Postcryotherapy Dellen Formation in Diabetics with Proliferative Retinopathy

MICHAEL NEWTON, M.D., AND KEITH M. ZINN, M.D.

Dellen are areas of peripheral corneal thinning occurring in regions of tear film instability and drying. Many processes causing elevation of the limbal conjunctiva may result in such corneal dehydration, including cataract and glaucoma surgery, pterygium, suture granuloma, limbal tumor, subconjunctival hemorrhage, and episcleritis (1). Cryosurgical treatment for glaucoma has been reported to cause dellen when direct corneal icing is experienced (2). We report here two cases of corneal dellen formation resulting from cryotherapy for diabetic retinopathy. There was no direct corneal freezing and only minimal diffuse conjunctival elevation in these patients. In case one, corneal scarring resulted; in case two, the clinical picture was consistent with limbal herpetic epitheliopathy.

Case Reports

Case 1. A 28-year-old white diabetic woman with "blurred vision" in the right eye of several days' duration was first examined in June 1981. The patient's best corrected visual acuity was 20/30 in the right eye and 20/20 in the left eye. The intraocular pressures and anterior segments were essentially within normal limits in both eyes. The vitreous cavities were grossly clear bilaterally. The optic nerveheads were within normal limits (OU) and the vein:artery ratio, at the disc margin, was 4:2 OU. Dot and blot retinal hemorrhages and retinal microaneurysms as well as early retinal neovascularization (proliferative diabetic retinopathy) were present in both eyes.

The patient underwent a series of panretinal argon laser photocoagulation treatments in both eyes which appeared to initiate regression of the retinal neovascularization in both eyes. The retinal status remained stable for 18 months. The patient became pregnant and in the seventh month of the pregnancy, the retinal neovascularization began to recur and progress in both eyes, more so in the left than in the right eye. Additional panretinal laser photocoagulation was delivered to both eyes, with mixed results. The right eye quieted down with stabilization of the retinal neovascularization. However, repeated vitreous hemorrhages developed in the left eye. The patient delivered a normal infant, but the vitreous hemorrhage persisted in the left eye.

At this point, the patient underwent a series of panretinal cryopexy treatments (without conjunctival incisions) in the left eye. Postoperatively, there was some perilimbal conjunctival swelling and a dellen formed secondarily (Fig. 1). The dellen was treated with hypertonic saline eye drops during the day and lid closure at night. Eventually, the dellen cleared, along with the bulbar conjunctival edema in the left eye.

Case 2. A 53-year-old white man with diabetes mellitus of at least 18 years' duration was first seen in April 1981. The patient also had a 15-year history of systemic hypertension and a history of bilateral recurrent vitreous hemorrhages, laser photocoagulation and panretinal cyropexy surgery (OU) in the two years preceding the date of our initial examination.

The ocular examination in April 1981 revealed a best corrected visual acuity of no light perception in the right eye and 20/200 in the left eye. The anterior segments were clear and unremarkable except for a 4+ dense cataract in the right eye, precluding any view of the vitreous, retina, choroid or optic nerve structures in that eye. There was a 2+ cataract in the left eye. The intraocular pressures were 26 mm of Hg in the right

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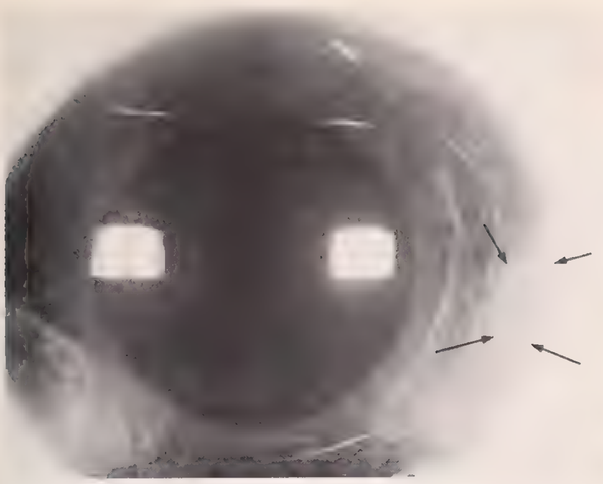

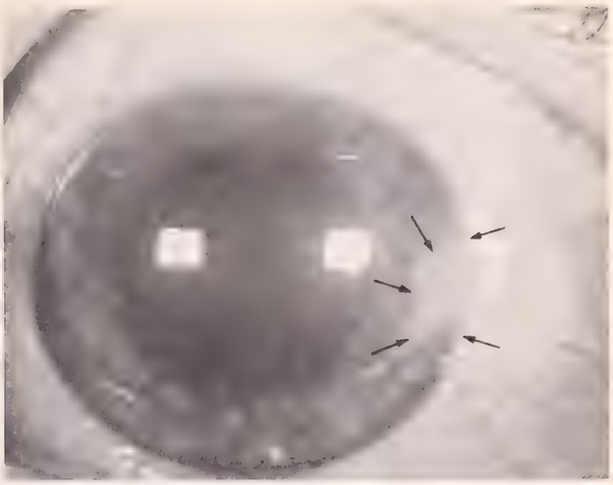

Fig. 1. Case 1. Left Dellen formation (arrows) after panretinal cryopexy in left eye. Note thinning and opacification of cornea.

Fig. 2. Case 2. Right Dellen formation (arrows) after panretinal cryopexy in left eye. Note thinning of cornea.

eye and 12 mm Hg in the left eye by applanation tonometry. The pupil of the right eye showed a Marcus Gunn response; normal pupillary reactions were found in the left eye.

In the left eye, the vitreous cavity had hemorrhagic debris present. Proliferative diabetic retinopathy with a perimacular traction retinal detachment was noted in the left eye. Numerous argon laser photocoagulation scars were noted peripheral to the macula and nasal to the optic nervehead OS. Several chorioretinal scars from previous cryopexy surgery were noted in the retinal periphery OS.

Because of the poor view due to moderate vitreous hemorrhagic debris in the left eye, the argon laser could not be used. Therefore, panretinal cryopexy surgery (without conjunctival incisions) was carried out to obliterate the peripheral retina. Postoperatively, there was perilimbal bulbar conjunctival edema with the formation of a corneal dellen OS. The left eye was treated with hypertonic saline solutions during the day and with lid closure at night. The dellen and bulbar conjunctival edema subsequently cleared over the next several weeks. The presenting dellen lesion was not typical and the possibility of a limbal form of herpes keratitis was considered, but viral cultures were negative.

Discussion

Corneal complications following intraocular surgery for vitreoretinal disease are well documented (3–5). Problems such as corneal edema and persistent epithelial erosions may be sight-threatening. Corneal problems related to noninvasive retinal cryotherapy are, however, not well known. That the two cases reported here occurred in diabetics confirms earlier reports that these patients are especially susceptible to corneal damage (3–5).

The corneas of diabetics have been found to be abnormal by many investigators. Problems such as epithelial basement membrane defects (6), decreased corneal sensitivity (7), metabolic alterations (8), and increased corneal thickness (9) have been well documented. The minimal conjunctival disruption that led to the dellen formation in our patients may reflect this inherent corneal instability.

The patients discussed above responded to conservative measures, including tear replacement and nightly lid closure. However, scarring has resulted in Case 1. In Case 2 the lesion presented with very significant corneal thinning and a clinical picture resembling limbal herpes simplex keratitis. The precise corneal abnormalities that make diabetics susceptible to these complications need further elucidation and the fragile nature of the diabetic cornea should be kept in mind when surgical manipulation is contemplated.

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Radiology Notes

Jack G. Rabinowitz, M.D., Editor

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Case 1

SHELLEY K. CHARNOFF, M.D.

Case Report. A four-year-old girl, previously in good health, sustained neck pain of sudden onset. She had no recent history of trauma, fever, cough, or infection. A tine test done one year prior to admission was negative. Aspirin therapy was initially administered, with no decrease in symptoms. The pain then spread to involve both arms, and two days later she was admitted to the hospital.

On examination, the patient had only limited range of motion in the neck, and mild, diffuse weakness in the right upper extremity. Complete blood count, electrolytes, sedimentation rate, and serum magnesium and calcium were all within normal limits.

Anterior-posterior and lateral views of the cervical spine revealed compression deformity of C4 (Fig. 1). The normal cervical lordosis was straightened. The adjacent intervertebral disc spaces were intact, and no paravertebral soft tissue mass was present. A skeletal survey showed a "bone-within-bone" appearance involving the vertebral body of L4 (Fig. 2). The left side of the vertebral body was more severely involved than the right. The remaining osseous structures were intact. Subsequent computerized tomography scan and bone scan supported the plain film findings, and did not reveal additional lesions. A biopsy of the L-4 lesion was performed.

Discussion. The differential diagnosis included eosinophilic granuloma, metastatic disease, infection, unrecognized trauma, and leukemia. The preservation of disc spaces, lack of soft tissue mass, and absence of any evidence of primary tumor excluded most of the latter entities and in light of the lumbar lesion, eosinophilic granuloma became the most likely consideration.

Eosinophilic granuloma is at the benign end of a spectrum of diseases classified under the general heading of histiocytosis X. All these lesions share the same underlying pathologic process (1): an abnormal proliferation of lipid-containing histiocytes within the reticulo-endothelial system.

Classification of a case in spectrum generally depends upon the age of onset, the original systems involved, and the course of the disease. Letterer-Siwe disease occurs in infants less than two years of age, and typically runs a rapidly progressive malignant course. Hand-Schuller-Christian disease is a more chronic form and occurs in children less than five years old. The classic triad of exophthalmus, diabetes insipidus, and "geographic" skull lesions is found in less than 10% of cases (2).

Eosinophilic granuloma most commonly affects boys between the ages of three and twelve (3). The pathologic changes are generally limited to bone. The lung, however, is also occasionally affected (4).

Vertebral involvement occurs in three phases (2). The earliest lesion is a destructive area in the center of the vertebral body. This is rarely observed on the radiograph, since collapse of the vertebral body into either a wedge-shaped deformity or a completely flattened "vertebra plana" ensues rapidly. This feature is almost always accompanied by the symptom of pain. The vertebral body is radiographically dense due in part to the compression of the trabeculae. In some instances the anterior margin of the collapsed body extends beyond the corresponding margins of the adjacent vertebral bodies. The pedicles are typically not involved. The adjacent intervertebral disc spaces are well maintained, and a paravertebral soft tissue mass is generally absent (5). These factors help differentiate eosinophilic granuloma from infection and tumor.

The final phase is a regenerative one, in which the vertebral body regains some and occasionally

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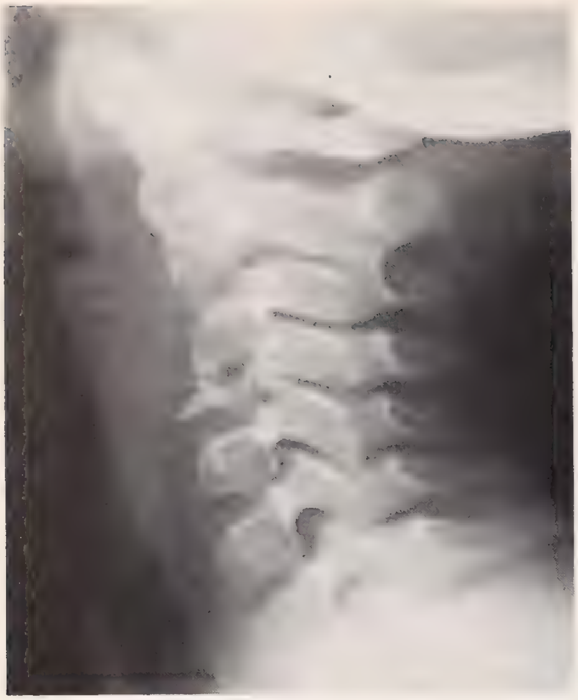

Fig. 1. Cervical spine demonstrates collapse of C4. Disc spaces are well maintained; some reversal of usual lordosis.

all of its initial height. In our patient, a residual sclerotic area remained within the regenerating vertebral body, producing a bone-within-bone appearance. Adjacent vertebral bodies are affected when more than one body is involved in a single patient (5). Of all the bones involved, the cervical spine seems to be the least commonly affected; the lumbar region is the most common (1, 5, 6). In one report in which seven vertebral lesions were encountered in six patients the cervical spine was not involved (1). In a larger series of 35 vertebral lesions, only 3 involved the cervical region (5). Of further interest is the complete absence in the literature of a report of the simultaneous existence of lesions demonstrating two opposing phases, active and completely healed. In view of the natural course of this disease process, one might expect to encounter this presentation fairly commonly. A healed lesion associated with a collapsed vertebral body is of diagnostic significance, as it adds greater credence to the diagnosis of eosinophilic granuloma.

Several studies have convincingly demonstrated reconstitution of vertebral body height following complete collapse (1, 5–7). If the lesion remains asymmetrical a high incidence of scoliosis may occur. A "bone-within-bone" deformity, observed in our patient, seems somewhat strange but has been known to occur (5). It probably does not represent a simple optical appearance but an actual residual sclerotic density within the reconstituted body.

Our patient demonstrated both typical and

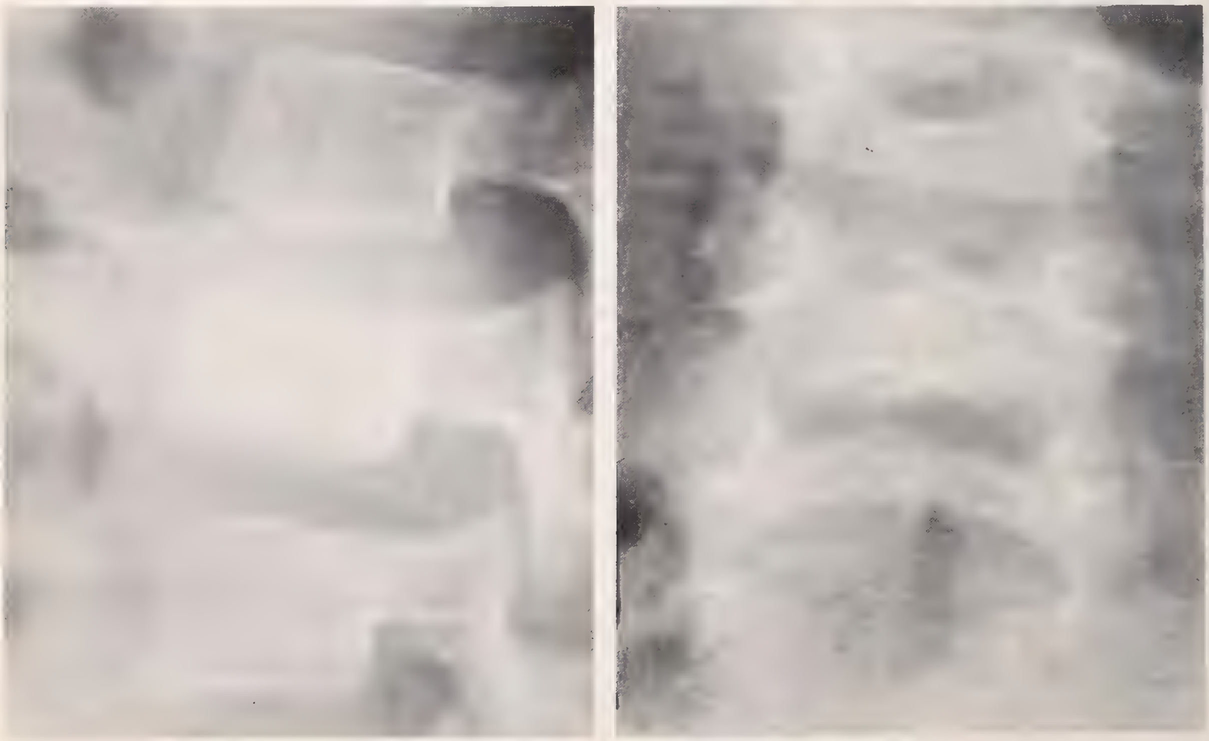

Fig. 2. Bone-within-bone appearance, of L-4, demonstrated in lateral view (**left**). Seemingly asymmetrical body (frontal view, **right**), although closer observation reveals almost complete reconstitution; no abnormal curvature.

atypical features of eosinophilic granuloma of the spine. In general, vertebral involvement is not confined to one area of the column, but when multiple vertebral bodies are involved they are usually adjacent (5).

Diagnosis: Eosinophilic granuloma of spine, multicentric and biphasic.

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Radiology Notes

Jack G. Rabinowitz, M.D., Editor

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Case 2

JERROLD T. GALE, M.D., AND DANIEL SCHLUSSELBERG, M.D.

Case Report. A boy aged 2 years three months was admitted to hospital after three weeks of diarrhea, fever to 101.2°F, and a painful right hip. A radiograph nine days prior to admission revealed a well-defined lytic lesion in the supraacetabular region of the right iliac bone (Fig. 1). On admission, the boy had slight tenderness over the right hip, without evidence of swelling. The white blood cell count was 11,900 and ESR was 56.

Intravenous antibiotics were begun. Repeat radiologic examination of the pelvis eleven days after the initial radiograph revealed a permeative lytic process involving the right iliac wing (Fig. 2). The lytic lesion appeared less well defined. A bone scan showed an intense uptake in the right iliac wing (Fig. 3). A bone marrow aspirate revealed a normal marrow, without the presence of tumor cells. No organisms were grown on culture. An open biopsy of the right ileum was performed and a cystic lesion in the supraacetabular region was seen. Histologic examination revealed destruction of bone tissue by a cellular infiltrate composed of polymorphonuclear cells, multinucleated giant cells, and numerous eosinophilic polymorphonuclear leukocytes (Fig. 4). The changes were consistent with eosinophilic granuloma.

Discussion. Eosinophilic granuloma of bone occurs in the first two decades of life (1), and is more commonly found in males (2). Flat bones are more frequently involved than cylindrical bones and the skull is the most frequent location, although the pelvis is also a common site (3–5).

One of the earliest descriptions of eosinophilic granuloma of bone was in 1940, by Otani and Ehrlich (6). Examination of a group of solitary lytic bone lesions in young persons revealed granulomas composed of giant cells, macrophages, and enormous numbers of eosinophils. The lesion was termed "solitary granuloma of bone." That same year Lichtenstein and Jaffe described lesions with similar radiographic and pathologic characteristics and called them "eosinophilic granuloma of bone" (7).

The name "histiocytosis X" was later applied as a broad designation of three different but interrelated entities: Letterer-Siwe (the most malignant variety), Schuller-Christian (the more chronic), and eosinophilic granuloma (the most benign and localized) (8). The bone lesions of eosinophilic granuloma are usually solitary and the radiographic characteristics have been well described.

The main feature is a sharply defined, oval or punched-out lesion due to destruction of the medullary canal. Occasionally, the margins are ill-defined. Many cases demonstrate cortical destruction and bone expansion has been known to occur. Periosteal reaction is common in long bones but unusual in flat bones (9).

The case presented is unusual because of the change in radiographic appearance, suggesting rapid progression of the lesion. The solitary well-defined lytic lesion seen early in the patient's course seemingly spread diffusely to involve the entire iliac wing within eleven days. This was thought to suggest an infective process.

The supraacetabular location of this patient's lesion is typical. In the pelvis the supraacetabular area, the ischiopubic rami, and the region adjacent to the sacroiliac joint are noted sites of predilection (5).

Also typical was the intense uptake of radionuclide on bone scan. However, radiographs are still considered more sensitive in the detection of lesions (10).

Diagnosis: Eosinophilic granuloma of pelvis progressing unusually rapidly.

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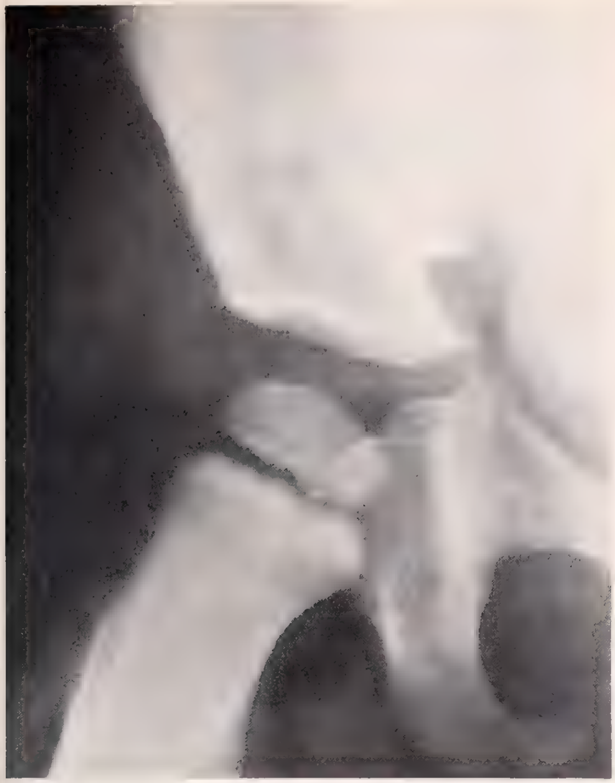


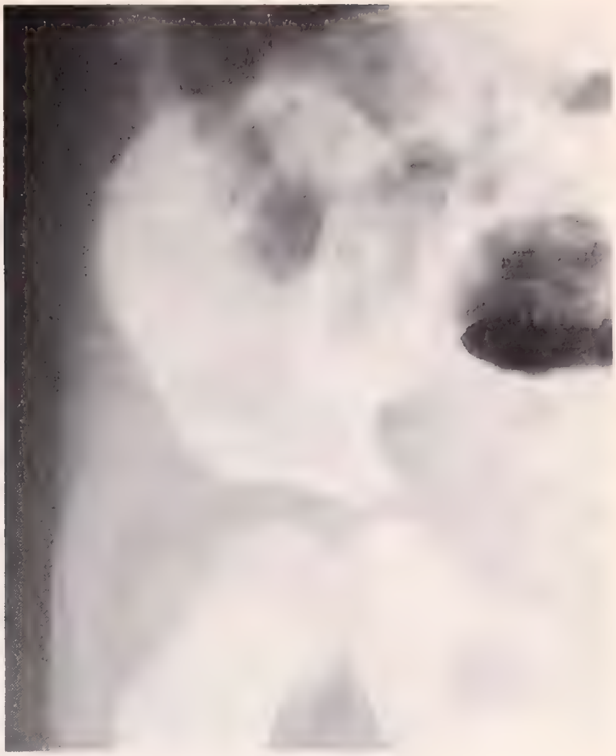
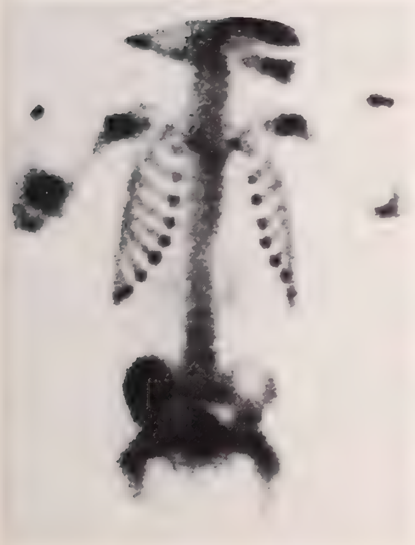


Fig. 1. Left Initial examination of right hip demonstrates well-defined cystic lesion within supraacetabular region.

Fig. 2. Right Eleven days later, borders of lesion appear less well defined and streaky changes are present in ilium (infiltration?).



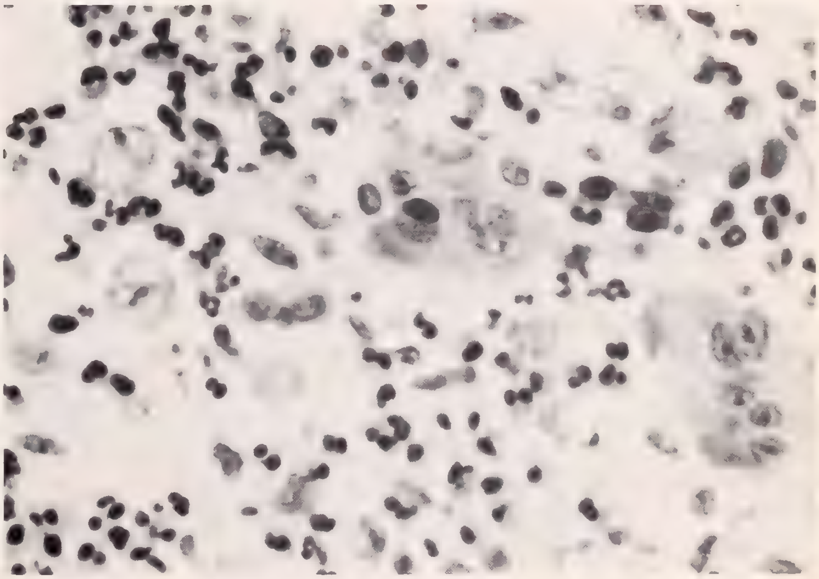


Fig. 3. Left Right ilium demonstrates intense uptake on scan.

Fig. 4. Right Microscopic section of lesion shows foci of histiocytes, some multinucleated; varied number of eosinophils and lymphocytes.

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Surgical Pathology Notes

Ira S. Schwartz, M.D., Editor

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This section, Surgical Pathology Notes, is planned as a regular feature of this journal. Case reports of particular interest will be presented, with documentation of the pathological findings, clinical correlations, differential diagnosis, and a brief review of the relevant literature.—ISS

Solitary Cecal Ulcer due to Cytomegalovirus in a Leukemic Patient

ELISE M. ROSEN-LEVIN, M.D., AND IRA S. SCHWARTZ, M.D.

Abstract

Solitary ulcerations are extremely unusual in the lower gastrointestinal tract. We report a case of solitary ulcer of the cecum associated with and apparently etiologically related to cytomegalovirus infection in an immunosuppressed patient with leukemia. A review of the literature and the implications for treatment are discussed.

Case Report. A 29-year-old woman with an 8-year history of chronic myelogenous leukemia developed brisk gastrointestinal bleeding (bright red blood from the rectum) while being treated for blast crisis. Splenectomy had been performed 3 years previously. The patient had been having intermittent spiking fevers ranging to 102°F and was being treated with hydroxyurea. She had previously received cytosine arabinoside and a nitrosourea (CCNU). Despite white blood cell counts of 45,000 (70% blasts), she refused medications other than hydroxyurea (25 mg/day). With this regimen the white blood cell count had fallen to 4000, but blasts were never completely eliminated. Initial study of the upper and lower gastrointestinal tract (endoscopy and technetium bleeding scan) showed no localized bleeding site. Melanotic stools continued, however, requiring multiple transfusions of packed red blood cells over the next month. The hematocrit initially dropped from 30% to 16% and was stabilized in the low twenty range. Angiography showed a large blush in the area of the cecum (Fig. 1). Resection of a 25-cm ileocolic segment was performed.

Pathological Findings. A large single ulcer of the cecum measuring 3.0 × 1.8 cm was found 5 cm distal to the ileocecal valve. The ulcer had a sharply circumscribed punched-out border with an erythematous rim. The necrotic base of the ulcer did not penetrate the muscularis propria. Otherwise, the small and large bowel were unremarkable (Fig. 2). Microscopically, the ulcerated mucosa was infiltrated by segmented leukocytes, small mononuclear cells, and large cells containing nuclear and cytoplasmic inclusions characteristic of cytomegalovirus (Fig. 3A). Inclusion-bearing, swollen endothelial cells were also identified (Fig. 3B), as were similarly affected smooth muscle cells of the muscularis mucosae (Fig. 3C). No inclusion-bearing cells were found in sections from nonulcerated portions of the bowel. A single small artery within the submucosa showed intimal proliferation with marked luminal narrowing and destruction of the internal elastic lamina. Leukemic infiltration was not found.

Clinical Follow-up. The patient tolerated the abdominal surgery relatively well. She developed

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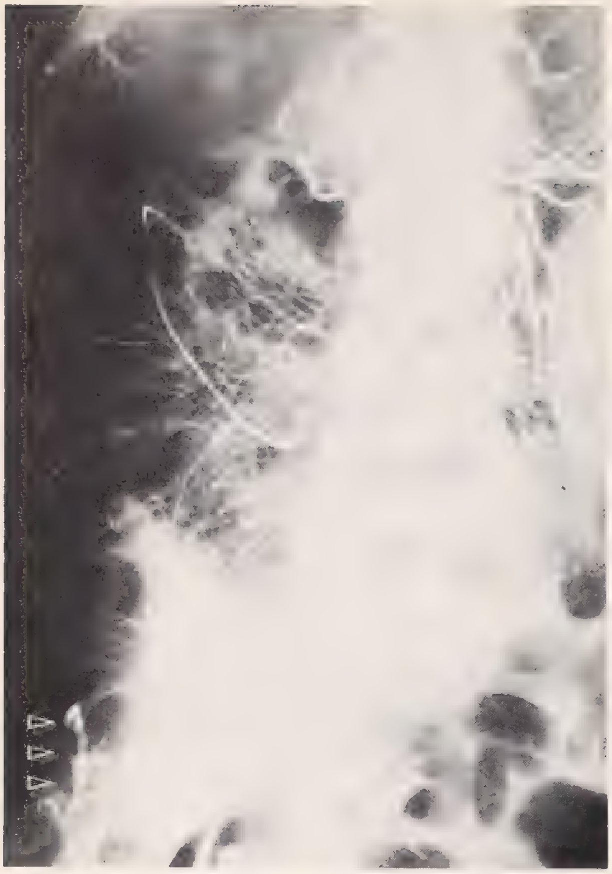

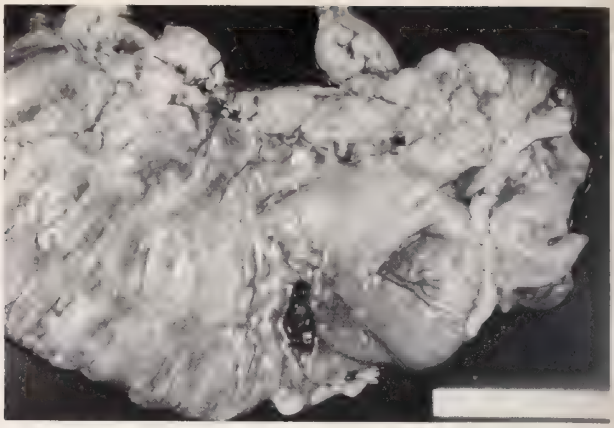

Fig. 1. Left Mesenteric arteriogram showing extravasation of contrast in region of cecum.

Fig. 2. Right Resected ileocolic segment with solitary, sharply punched out ulcer in cecum.

respiratory failure with pulmonary infiltrates which were unresponsive to antibiotics. Terminally, seizures occurred and an intracranial mass lesion which had been present on computerized tomography scan prior to the gastrointestinal bleeding was noted to persist. Central nervous system leukemic infiltration had never been demonstrated. No autopsy was performed.

Discussion. Solitary ulceration of the large intestine is an extremely unusual event, as evidenced by the paucity of case reports (1–6). The clinical presentation is usually that of lower gastrointestinal bleeding, often of exsanguinating proportion. Approximately 50% of isolated large bowel ulcers occur in the cecum. Susceptibility of the cecum to inflammation (typhlitis) has been explained by decreased vascular perfusion secondary to distensibility, stasis, and decreased motility (5). By far the most common cause of cecal ulceration is primary adenocarcinoma. Radiologically benign and malignant cecal ulcers are easily confused, especially since the former are statistically so rare. Other causes of lower intestinal ulceration and hemorrhage to be considered in the differential diagnosis are secondary malignant infiltration (leukemia, lymphoma, metastatic carcinoma, or melanoma), infection (bacterial, fungal, viral), coagulopathy, vasculitis, and vascular malformations.

The presence of localized cytomegalovirus (CMV) infection in the base of the cecal ulcer suggests an etiologic relationship. CMV has a proclivity for endothelial cells and has been shown to be associated with vasculitis at many sites (7). Endothelial involvement may result in ischemic damage with resultant mucosal ulceration and hemorrhage.

Cytomegalovirus is a member of the herpes family. It rarely causes significant illness in immunocompetent individuals, but has become an important infectious agent in immunosuppressed individuals. These include patients with leukemia and other malignancies, particularly those receiving cytotoxic, immunosuppressive, and steroid therapy (8). Transplant recipients, patients with acquired immunodeficiency syndrome (AIDS), infants, children, and the elderly are also at risk.

The common presentations of CMV-associated illness are pneumonia and heterophile-negative infectious mononucleosis. The histologic identification of CMV inclusions requires a high index of suspicion, especially if only a few infected cells are present or extensive necrosis has occurred (7, 9–11). Culture of CMV is now routinely available in many laboratories and is a more sensitive method of diagnosis (12). Treatment of the underlying factor (i.e. cessation of immunosuppressant therapy), while vital, may not be feasible or sufficient to effect cure. Limited success with antiviral agents such as Ara-C has been reported (13). CMV ulcerations of the gastrointestinal

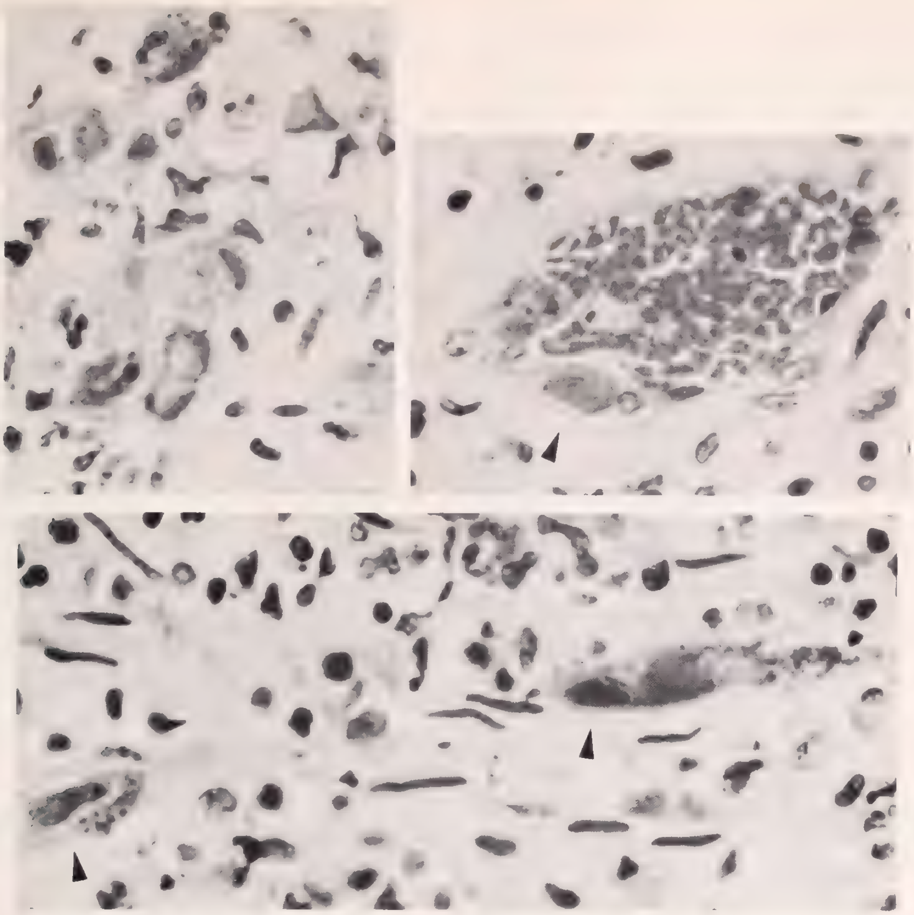

Fig. 3. Photomicrographs depicting CMV affected cells: **(A, above left)** within the ulcerated mucosa, as a cluster of cells among inflammatory cells, **(B, above right)** vascular endothelium **(C, bottom)** in smooth muscle cells of muscularis mucosae (hematoxylin and eosin stain, ×400).

tract may require surgical intervention in order to avert fatal hemorrhage or perforation, which are the most serious complications (3).

Acknowledgments

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Students' Corner

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Postoperative Pain Control: Review of Methods

SCOTT A. BERGER, M.D.

The traditional method of postoperative pain control has been intermittent injections of morphine or some other narcotic. In addition to troublesome systemic side effects, this form of analgesia is frequently criticized for being inadequate and inconsistent because of variations in absorption. Other methods of pain control have been shown to offer alternative, often superior analgesia with less troublesome side-effects.

Improved analgesia in the postoperative period can reduce subjective pain and decrease the incidence and severity of its accompanying problems. The more significant of these problems include respiratory complications, venous stasis and embolization due to delayed ambulation, and gastrointestinal dysfunction (1).

Pain is a highly subjective sensation, determined by both the sensations reaching the central nervous system and the way in which the stimuli are perceived (2). The degree of surgical trauma, the type of operation performed, and the patient's psychological profile can all influence the amount of pain experienced. One study showed that one third of surgical patients derived as much relief from placebos as from 10 mg of morphine, and that the tendency to find relief from placebos increased as the amount of pain increased (3).

Somatic pain is associated with damage to skin, fascia, muscles, pleura, pericardium, and peritoneum. Somatic sensation is transmitted along anterior and posterior rami of spinal nerves that penetrate from the surface inward (4). The pain is generalized over the affected area.

Visceral sensation is transmitted along afferent nerves that primarily run continuous with sympathetic nerve trunks (some exceptions include afferents from pelvic structures and the esophagus that run with parasympathetic fibers) (5). The site at which a particular sympathetic ganglia attaches to the anterior ramus of a spinal nerve may be far from the actual source of pain. Visceral pain is thus often said to be "referred." The dermatome to which visceral pain is referred is related to the segment of the embryo from which the visceral organ derives.

I review here the recent literature comparing different methods of postoperative pain control.

Narcotics

Systemic use of narcotics, either intramuscular or intravenous, is the most common method of postoperative pain relief. Morphine continues to be the prototype against which all other narcotics are measured. Like other narcotics, morphine's analgesic effects are due to its effects at multiple sites within the central nervous system (6). Unlike regional anesthetics, systemic narcotics do not impair conduction of nerve impulses along peripheral nerves, nor do they alter the threshold of noxious stimulation to nerve endings. Pain is still recognized, but is perceived as being less intense. In addition to their analgesic effects, narcotics produce sedation and euphoria, both of which can be beneficial in relief of pain.

Adverse Effects. The most troublesome of the physiologic and dose-related side effects of narcotics is respiratory depression, mediated by decreasing the sensitivity of the medullary center to CO_2 (2, 6). The cardiovascular effects of narcotics are essentially those of postural hypotension, and are somewhat more significant for morphine than meperidine. Other notable side effects include nausea and vomiting, constipation, urinary retention, and pruritus. Of particular risk in the postoperative period is suppression of the

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cough reflex, since failure to clear the lungs can predispose the patient to atelectasis and other respiratory complications.

Synthetics and Antagonists. The only synthetic narcotic to achieve widespread acceptance is meperidine. Its analgesic and systemic effects are considered comparable in most respects to morphine. In addition, its shorter duration of effectiveness and slightly less spasmogenic effects on smooth muscle make it preferable to morphine in certain clinical applications.

To date synthetic narcotic antagonists, such as pentazocine, have not been found to provide strong analgesia without the unwanted side effects of narcotics. Among the newer drugs, buprenorphine seems to hold the greatest promise, but needs further evaluation (3, 7).

Administration. Postoperative pain relief most often involves the administration of morphine or meperidine over the first 24–48 hours when the pain is most severe. When the patient can tolerate liquids, this narcotic administration is followed by codeine, acetaminophen, or aspirin.

Absorption Problems. The optimal dose for a 70 kg patient is 10 mg morphine or 80–100 mg meperidine (3, 8). Much of the poor control of postoperative pain is caused by the inadequacy and fluctuation of plasma drug concentrations, compounded by variable absorption from the intramuscular site. As expected, plasma concentrations reflect the periodicity of intermittent injections (1, 8, 9). Austin et al confirmed that a relationship does exist between plasma concentrations and analgesic effect following intramuscular injections (9). They determined the minimum analgesic concentration (MAC) for meperidine to be 0.5 ± 0.1 μg/ml. However, the first postoperative 100 mg injection never attained a plasma concentration sufficient to produce adequate analgesia. Subsequent injections resulted in plasma concentrations that fluctuated above and below the MAC. During each four-hour dosing interval, plasma concentrations of meperidine were greater than the MAC only 35% of the time.

The variability of duration of intramuscular narcotic injections indicates that many patients will be in extreme pain while waiting for their next dose. It has been demonstrated that smaller doses of narcotics can achieve greater analgesic effect if given before the onset of severe pain, by slowly titrating the drugs intravenously to determine the patient's individual needs, or by recording the duration of the first two doses given intramuscularly and administering further doses at regular intervals shorter than the duration of analgesia (1, 7).

Continuous Infusion. Clearly, the most constant level of systemic analgesia would be provided by a continuous infusion of narcotics. Using continuous low-dose infusion analgesia, Stapleton (10) reported an MAC for meperidine (pethidine) of 0.46 μg/ml, which correlated well with the MAC reported by Austin (9). Pain persisted approximately 4–5 hours until the MAC of 0.46 μg/ml was reached. Thereafter, patients were without pain until 5 hours after the 32-hour infusion had ceased. Side effects, even at concentrations of 0.6 μg/ml, were minimal and most patients were alert and comfortable. The amount of meperidine used by Austin (100 mg 4h intramuscularly) and Stapleton (100 mg continuously over 4 hours) was the same, indicating that the differences in blood concentrations and analgesia were due to differences in absorption.

Rutter (12) compared the analgesic effects of morphine given continuously, intramuscularly every 4 hrs, and intramuscularly as needed. Continuous intravenous morphine produced better analgesia, with better respiratory function, and lower total dosage than the other methods. The improvement in vital capacity and pulmonary expiration function tests was believed to represent an objective measure of pain relief (the ease in breathing deeply and coughing) rather than a central respiratory effect.

On-Demand Analgesia. Although continuous intravenous analgesia may well represent a real advance in postoperative pain control, the threat of overdosage is ever present and careful patient monitoring is needed. An alternative technique, and one that should prove less dangerous, is the use of "on-demand" analgesia or self-administered intravenous infusion, arranged so that the patient is prevented from exceeding a harmful upper limit. However, Welchew (8) reported that overall pain relief, using on-demand fentanyl, though somewhat more constant than intramuscular morphine every 4h, did not provide complete analgesia and offered no significant improvement in analgesia or respiratory function. Previous reports to the contrary did not arise from "pure" on-demand analgesia but from continuous low-dose narcotic infusions, supplemented by on-demand bolus injections of narcotics (13, 14). The cost of infusion pumps and on-demand computer systems will necessarily limit their application to select patient populations.

Regional Anesthetics

In regional anesthesia, local anesthetics are used to interrupt neural conduction along nerve fibers in the central and peripheral nervous systems. The anesthetics act by inhibiting sodium permeability and therefore interfering with membrane depolarization (15).

Adverse Effects. Regional anesthetics can be thought of as peripheral and central (epidural and spinal). The most common side effects of local anesthetics, usually seen with peripheral nerve blocks, are dose-related and include central nervous system toxicity and hypotension (16). The addition of epinephrine to the anesthetic solution slows the absorption of the anesthetic into the blood, thereby decreasing the risk of systemic effects and increasing the duration of the anesthetic agent (15). Many of the reactions commonly seen with local anesthetics (anxiety, tachycardia, tremors, and sweating) are in fact actually due to the epinephrine. Consequently, epinephrine must be used with special caution in patients with high blood pressure, peripheral vascular disease, and arrhythmias.

Intercostal Block. The intercostal block, initially developed for surgical anesthesia, was one of the few peripheral nerve blocks applied frequently for postoperative pain control (17). This block provides good analgesia without the sedation or respiratory depression produced by narcotics. It is effective for the relief of somatic pain in the chest and abdomen (3). Compared with central anesthesia this block causes no physiologic hypotension or retention of urine. Both methods permit coughing and deep breathing without pain, unlike narcotics. However, unlike central anesthesia, intercostal block does not block visceral pain fibers. Nonetheless, with its short duration of effect and risks of toxicity and pneumothorax, intercostal blocks are unlikely to enjoy much popularity in the future, especially with the increased usage and success of the central nerve blocks.

Central Anesthesia. Epidural anesthesia involves the injection of anesthetics into the epidural space, blockading the spinal roots. In spinal anesthesia, the anesthetic is injected directly into the subarachnoid space, blockading the spinal cord itself.

Effects. The actions, mechanisms, and physiologic effects of both spinal and epidural anesthetics are similar. Central nerve blockade is capable of producing segmental loss of autonomic, sensory, and motor function. For a given level of sensory block, sympathetic block is approximately 2–3 segments higher; motor block is 2–3 segments lower (15, 16). In contrast to systemic narcotics, central blockade can not only provide complete somatic and visceral analgesia, but can also interrupt reflex responses as well (1). Patients have improved respiratory function and less gastrointestinal dysfunction, are alert and cooperative, and ambulate early, usually with little loss of motor function (3, 18).

Physiologic Hypotension. Unlike the hypotension that is produced by toxic levels of anesthetic in peripheral blockade, the hypotension in central blockade is physiologic and produced by inhibition of sympathetic conduction. The higher the level of the block, the greater the degree of hypotension. With proper hydration, use of pressor drugs when necessary, and skillful anesthesia technique, the risks of hypotension can usually be minimized.

Most postoperative pain control using central nerve blockade has involved epidural anesthesia. Compared with spinal anesthesia, epidural anesthetics produce less profound hypotension and have less potential risk of lumbar puncture headaches and neurological complications (16). The onset of epidural anesthetics is usually rapid, occurring in most cases within 10–15 minutes. Duration of anesthesia is variable: lidocaine, 60–180 minutes; bupivicaine, 3–6 hours (14). In addition to its relatively longer duration, bupivicaine delivers the most sensory blocking with the least motor blocking, and is considered by many authors to be the drug of choice for epidural anesthesia (18, 19).

Continuous Infusion. Continuous epidural infusions offer the advantages of epidural anesthetics over indefinite periods of time. They have been shown to produce good analgesia; most patients require little or no additional epidural bolus or narcotic supplements for control of pain (19, 20). In addition, few complications and no evidence of anesthetic accumulation in the epidural space or bloodstream have been reported.

Problems. Aside from the physiologic effects of hypotension and motor blockade, complications of epidural anesthesia include urinary retention and decreased rectal function (if the sacral segments are blocked), infection, broken needles, and accidental subarachnoid injection. The latter is the most feared, since it may cause high spinal anesthesia with respiratory paralysis and circulatory depression (14, 16).

Epidural and Intrathecal Narcotics

Epidural and intrathecal narcotics provide powerful and prolonged analgesia, without the systemic side effects of parenteral narcotics or the hypotension produced by sympathetic blockade that is characteristic of regional anesthesia.

Mechanism. Most research supports the notion of a direct spinal action of intrathecal and epidural narcotics (17, 23–31). Opiates are believed to act at specific receptor sites within the substantia gelatinosa of the dorsal horn of the spinal cord. Naloxone injected intravenously is known to reverse the sedative and respiratory-depressive effects of epidural narcotics with little or no change in analgesia (27, 30, 32). In addition, plasma levels significantly below the minimum concentrations said to be necessary for analgesia using parenteral narcotics have been shown to produce a prolonged and intense effect following epidural injection (27, 29, 33). Finally, the administration of epidural morphine has been shown to produce a segmental analgesia (31).

Epidural narcotics have enjoyed greater popularity than intrathecal narcotics for most of the reasons discussed with regional anesthetics. There is less risk of complications, and the less profound physiologic effects allow greater control.

Onset and Duration. Most studies have found that 2–4 mg morphine produces a mean of 16–21 hours of analgesia, and that the onset of significant analgesia usually occurs in 10–60 minutes. However, both time of onset and duration have been subject to wide variations (17, 25–27, 34, 35).

Comparative Studies. Rawal (17) compared patients receiving epidural morphine, intramuscular morphine, and intercostal block. Epidural morphine produced the best results, and intramuscular morphine the worst, in quality of pain relief, pulmonary function, incidence of postoperative vomiting, and duration of effect (Table 1). In addition, 40% of patients receiving epidural morphine required no additional analgesia during their hospitalization. Approximately 22% of patients in all 3 groups had transient urinary retention. There were no reports of hypotension.

Bromage (36) studied patients receiving intravenous narcotics, epidural anesthetics, and epidural morphine. Both epidural narcotics and epidural anesthetics provided superior and longer lasting analgesia than intravenous narcotics and were twice as effective in restoring postoperative pulmonary function. In comparing epidural narcotics directly with epidural anesthetics, it was found that the analgesia from the narcotics was longer lasting and lacked the effects of sympathetic blockade. However, the analgesia of the anesthetics was more intense and its systemic effects showed less variation, including the restoration of pulmonary function. It was felt that this could be of particular benefit in patients in whom management of severe pulmonary disease was crucial.

TABLE 1

Comparison of Epidural Morphine, Intercostal Block, and Intramuscular Morphine in Humans

	Epidural morphine	Intercostal block	Morphine *IM*
Mean duration/range (hrs) of analgesia	19.3/6–35	11.1/5–21	5.5/2.5–13
Patients describing pain relief as excellent	88%	71%	40%
Mean % decrease in pulmonary expiratory function	10%	25%	40%
Patients with postoperative vomiting	7%	23%	28%
Patients with urinary retention	22%	22%	22%

Continuous Infusion. Like epidural anesthetics, epidural narcotics have also been given successfully by continuous infusion. Welchew (37) observed superior analgesia, improved respiratory function, and clearer mentation in patients receiving continuous epidural fentanyl compared to those receiving intramuscular papaveretom. Minimal side effects were reported.

Respiratory Depression. The early literature contains numerous reports of unusual and delayed-onset respiratory depression following epidural injection of narcotics (7, 27–29, 34). Recent evidence, however (1, 33, 35), suggests that the respiratory depression associated with epidural morphine is similar to that seen with parenteral narcotics, and is a dose-related effect. Overdosage or idiosyncratic reactions are believed to be the causes of previous reports of respiratory depression.

The respiratory depression following administration of intrathecal narcotics has been far more dramatic and may well represent a different mechanism. It is believed that high concentrations of narcotics in the cerebrospinal fluid reflux through the fourth ventricle, causing a direct depression of the respiratory center. In studies in which patients were kept in a head-up position and intrathecal narcotics were administered in a hyperbaric solution, respiratory depression was not encountered (32, 38).

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) has been used extensively in the treatment of chronic pain. The association of TENS with decreased narcotic usage has prompted considerable research into its possible role in postoperative analgesia.

Current Theories. The effect of TENS was originally based on the “gate theory of pain” proposed by Melzack and Wall in 1965 (39). The theory suggests that a spinal gating mechanism exists within the substantia gelatinosa of the spinal cord. Stimulation of the large, more excitable A-delta fibers is thought to close the gate and inhibit transmission of nociceptive impulses. Stimulation of the small C fibers is thought to open the gate. In addition, corticofugal (efferent) fibers also terminate in the substantia gelatinosa, where they too can inhibit transmission through the gate.

The gate theory has been challenged by some authors who believe that the effect of TENS is mediated by the electrically stimulated release of endorphins. Solomon et al (40) demonstrated that TENS was ineffective in patients chronically exposed to narcotics. These patients also responded poorly to large doses of parenteral analgesics. Patients who had no history of narcotic exposure did respond to TENS. These results suggested a common pathway for TENS and narcotic-produced analgesia. This was refuted by Abram (41), who demonstrated that the analgesia experienced by chronic pain sufferers receiving TENS was not reversed by intravenous naloxone. Unfortunately, neither study was able to demonstrate whether the effect of TENS could be produced by direct spinal action. Additional research still remains to be done in this area.

Effectiveness. TENS is a noninvasive procedure with no known complications and few contraindications (42, 43). Numerous studies have shown TENS to be effective in managing postoperative pain and reducing narcotic requirements, sometimes substantially (40–44). However, no objective, conclusive evidence has been offered that TENS has a true analgesic effect not attributable to the placebo effect. Nonetheless, the apparent improvement in analgesia, the decrease in narcotic requirements, and the established role of TENS in the management of chronic pain indicate that the use of TENS postoperatively undoubtedly warrants further evaluation.

Summary

Postoperative pain control most often consists of intermittent narcotic injections. Such analgesia is easily administered but is often inadequate and involves the risk of respiratory depression, hypotension, and other systemic side effects. Alternative analgesic techniques are discussed. Continuous intravenous narcotic techniques offer improved analgesia but are expensive, and concern exists about their potential for overdosage. Two similar approaches involve epidural and intrathecal administration of either anesthetics or narcotics. Compared to systemic narcotics, both techniques provide superior analgesia. Patients also have improved respiratory function and tend to ambulate earlier. The major disadvantage of the anesthetics is physiologic hypotension due to sympathetic blockade. The narcotics involve the risk of respiratory depression. Another technique shown to decrease postoperative narcotic requirements in certain clinical settings is TENS. Already established in the control of chronic pain, it has no known complications and few contraindications.

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Protein-Calorie Malnutrition, Immunologic Function, and Total Parenteral Nutrition in the Surgical Patient

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The nutritional status of the surgical patient has been implicated as a predisposing factor in postoperative morbidity and mortality partly because of its association with impaired immune function. The reported 50% prevalence of protein-calorie malnutrition in the hospitalized population of the United States underscores the potential magnitude of the problem (1, 2). Malnutrition and immune function are complex phenomena with many interacting components. The identification of elements of their interaction provides a mechanism for defining surgical patients at risk for increased morbidity and mortality because of nutritionally related immune deficiencies. Total parenteral nutrition (TPN) can be used to replete these patients preoperatively. Techniques for monitoring the immune status of the identified patients have been utilized to assess the success of preoperative nutritional supplementation as a mechanism for restoring immune function. The potential risks of TPN, the prolonged hospitalization it requires, and the increased cost involved make a demonstrable reduction in operative morbidity and mortality a prerequisite for its clinical use.

This paper will review the identification and prevalence of protein-calorie malnutrition, the morbidity and mortality associated with it, the elements of immune function affected by it, and the parameters used to monitor immune status. Finally, the ability of TPN to restore immune function and reduce morbidity and mortality in the surgical patient will be discussed.

Protein-Calorie Malnutrition

Surgical patients are subject to protein-calorie malnutrition preoperatively because of chronic debilitating diseases such as malignancies, inflammatory bowel disease, malabsorption syndromes, and many other gastrointestinal-related diseases. Additional metabolic deficiencies can result from surgical intervention and conventional postoperative intravenous fluid management. Postoperative complications such as intestinal fistulas or leaking anastomoses may result in prolonged periods of inadequate oral feeding for these patients (3).

The variety of factors affecting nutrition in the surgical patient makes categorizing possible types of protein-calorie malnutrition difficult. Baseline variability in the potential deficit of calorie sources of fat, skeletal muscle, and visceral protein adds to the problem of measurement and categorization.

Marasmus. Adult marasmus is produced when malnutrition results from the anorexia of disease. Most of the calorie deficit is made up by body fat and muscle (4); loss of muscle and fat is reflected in reduced body weight. Loss of body fat is also reflected in the triceps skinfold measurement. Arm muscle circumference signifies loss of skeletal muscle, the major protein reserve of the body. In purely adult marasmus, serum albumin, serum transferrin, and immune competence are believed to be well maintained (5).

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Kwashiorkor-Like Syndrome. The stress of infection or injury such as surgery produces a catabolic response which results in a gradual increase in protein loss and impaired visceral protein function. This is reflected in the finding of hypoalbuminemia and anergy (4, 5). Anthropometric measurements are maintained within normal limits initially but are eventually reduced (6). This condition is called hypoalbuminemic malnutrition by Bistrian et al (4, 5) and in etiology superficially resembles kwashiorkor seen in children. The major finding is hypoalbuminemia and it is generally not distinguishable by physical exam.

The mechanism of the hypoalbuminemia in this kwashiorkor-like syndrome is related to the insulin response to the combination of catabolic stress and carbohydrate intake (for instance, in surgical patients maintained on 5% dextrose). The insulin produced as a result of dextrose infusions and stress disrupts the normal metabolic response to injury by causing a reduction in peripheral fat and skeletal protein mobilization (4). Impaired visceral protein synthesis results from the decreased availability of amino acids from muscle sources.

The depleted visceral protein mass is reflected in the reduced rate of production by the liver of the transport proteins albumin, transferrin, and prealbumin (7). The significance of the transport protein depletion is dependent upon a steady-state condition without exogenous influences such as administration of protein products. Serum levels of albumin fall and recover slowly with changes in nutrition and are therefore considered a poor indicator of early protein malnutrition. Serum transferrin is considered to give a more accurate indication of acute changes in visceral protein levels because it has a smaller body pool and a shorter half-life. The very short half-life and small body pool of prealbumin makes it subject to rapid fluctuations in measurement.

Elements of both adult marasmus and kwashiorkor-like malnutrition may be found in the surgical patient. Frequent findings of deficiencies of vitamins, trace elements, minerals, and fatty acids also influence the clinical picture (8).

Protein Metabolism and Malnutrition. A consideration of the process of protein metabolism by the body clarifies the significance of protein-calorie malnutrition. Protein turnover consists of a continuous process of synthesis and degradation from exogenous and endogenous amino acids which, according to Millward and Garlick (9), accounts for 40% of the resting total body energy expenditure. This dynamic process enables a finite protein pool to be used with great variability for rapid shifts between its structural role and its use as hormones, enzymes, or immune-response mediator. The pattern of metabolic adaptation may be impaired if the supply of amino acids or energy is limited.

The diversion of amino acids from an endogenous metabolic role occurs when the supply of exogenous amino acid is insufficient. Low-priority reserves, such as the maintenance of muscle mass, are depleted at times of starvation or stress to benefit the supply of high-priority proteins important for survival. The protein pools for wound healing and the immune system are of high priority to which regulatory mechanisms will divert amino acids from functions of lesser importance, such as maintenance of muscle mass. Protein pool depletion because of serious malnutrition, disordered regulatory mechanisms, or an extreme demand like major surgery can disrupt the normal dynamics of protein metabolism. The protein metabolic capacity of the patient does not respond appropriately and the high-priority pools essential for survival will remain depleted (10).

The balance of amino acids and glucose necessary for the normal dynamics of protein metabolism following surgical stress is demonstrated in a study by Young and Hill. They evaluated the effect of glucose and infused amino acids on body composition and plasma amino acids following major rectal surgery. A comparison was made between patients receiving amino acid infusion alone and those receiving amino acids and glucose infusion. Amino acid infusion alone resulted in poor utilization of amino acids with muscle mobilization, gluconeogenesis, and increased acute phase proteins. There also was no synthesis of transport proteins in this state of energy deficit. Infusion of amino acids and glucose prevented body tissue loss and resulted in increased plasma proteins (11).

Prevalence. The magnitude of the problem of protein-calorie malnutrition in hospitalized patients has been demonstrated in several studies. Bistrian et al (1) reported a prevalence of almost 50% among hospitalized surgical patients among 131 patients evaluated as representative of general and specialty surgical services. Of this total, 48% were found to have protein-calorie malnutrition of varying severity as measured by the triceps skinfold and arm muscle circumference technique which correlated with diminished serum albumin levels. Another study by Bistrian (2) of general medical patients found the prevalence of protein-calorie malnutrition to be 44% or greater as measured by criteria which included triceps skinfold, arm muscle circumference, serum albumin, weight/height, and hematocrit. A British study by G. L. Hill (12) of 105 surgical patients found the frequency of low values for the indices used to test protein-calorie malnutrition (weight loss, arm-muscle circumference, plasma albumin, plasma transferrin) to be greater than 50% among patients remaining in the hospital for more than a week after major surgery.

Effect on Immune Function. The relationship of protein-calorie malnutrition to the immune system has been extensively studied in animal and human models; numerous studies have involved malnourished children (13, 14). The range of potential immune deficiencies which have been related to protein-calorie malnutrition includes elements of cell-mediated and humoral immunity, phagocytosis, and the complement system. In vivo and in vitro tests of immune function in the malnourished hospitalized adult population have been evaluated and correlated with morbidity and mortality rates. An evaluation of the contribution of malnutrition to altered immune response is complicated, however, by other suppressors of immune function which may interact in the patient. These include malignancy (15–18), drugs (19), chemotherapy and radiotherapy (20, 21), surgery and anesthesia (22–25), coexisting infections (26), and aging (27). An analysis of the function of the immune system must consider the potential importance of these variables to the immune response.

The significance of the deficiencies in immune response for the surgical patient is reflected in the major contribution made by infectious complications to morbidity and mortality (28). The wound, pulmonary, and urinary tract infections to which surgical patients are at risk may be facilitated and complicated by an increased susceptibility to septic involvement in the patient with impaired defense mechanisms (3). The infectious process itself can be implicated as a cause of diminished nutritional status. This process becomes a cycle: malnutrition, altered immune function, infection, worsening malnutrition (3).

Indications for Total Parenteral Nutrition. Total parenteral nutrition has provided a means for restoring immunocompetence in the patient who suffers from nutritionally impaired immune function. The use of parenteral nutrition to correct nutritional deficiency in the surgical patient is indicated when the gastrointestinal tract is unavailable for use or when the metabolic requirements of the patient for rapid nutritional repletion would be better satisfied by intravenous than by oral or enteral routes, for example in bowel obstruction, prolonged ileus, acute inflammatory bowel disease, hemorrhagic pancreatitis, the short-gut syndrome, burns, and multiple trauma. Parenteral therapy is recommended when bowel rest is desired in gastrointestinal fistulas and abscesses, inflammatory bowel disease, malabsorption syndromes, and intractable diarrhea. Enteral intake is contraindicated in hazardous conditions like relapsing coma or laryngeal incompetence, tracheoesophageal fistulas, and toxic megacolon. In patients undergoing chemotherapy or radiation therapy, appetite may be diminished; nausea, vomiting, abdominal pain, and diarrhea make the adequacy of oral nutrition unlikely (29). The use of parenteral nutrition is also indicated in the severely malnourished patient who is subject to morphologic, environmental, and absorptive abnormalities. Gastrointestinal columnar mucosal cells become cuboidal with a reduced brush border in severe malnutrition. There is decreased production and migration of mucosal cells, diminished GI motility, and bacterial overgrowth. This can result in protein, fat, and glucose malabsorption. Adequate enteral protein-calorie repletion can reverse these changes but initial poor absorption, nausea, diarrhea, bloating, and abdominal pain may slow the process. Total parenteral nutrition allows more rapid resolution of this condition (30).

Prediction of Morbidity

Mullen et al (31) evaluated a series of 64 consecutive surgery patients to determine if any statistically significant nutritional or immunologic criteria predictive of operative morbidity and mortality could be elicited to prospectively determine candidates for nutritional support. Serum albumin levels, serum transferrin, and delayed hypersensitivity reactions to test cellular immunity were the statistically significant factors of the 16 studied by Mullen as of possible value in predicting postoperative morbidity and mortality.

Serum albumin levels less than 3 gm/dl were found to be associated with a complication rate increased $2\frac{1}{2}$ times over levels greater than 3 gm/dl. Complications included wound infection, pneumonia, septicemia, wound dehiscence, respiratory failure, fistula, atelectasis, urinary tract infection, intraabdominal sepsis, pulmonary embolus, myocardial infarction, and death. Complications increased five times in patients with serum transferrin levels below 220 mg/dl. A 33% complication rate was found in those patients who were anergic, $2^1/_2$ times greater than in those reactive to at least one of three skin-test antigens. Septic complications were found to be the most common complication of malnourished patients in the study.

A flaw in Mullen's study is that no data are reported about the preexisting diseases in his patient sample; the consequences of various diseases and therapeutic measures on tests of nutritional and immunologic competence constitute an additional uncontrolled variable.

The relationship of serum albumin, serum transferrin, and anergy to operative morbidity and mortality as found by Mullen et al (31) is documented in other studies. A study by Seltzer et al (32) found a significant 4.6-times increase in complications in 263 surgical patients with abnormal serum albumin on admission. Using lymphocyte count as a measure of immunocompetency, Seltzer found a statistically significant 3.5-times increase in complications when both serum albumin and total lymphocyte count were below normal. Total lymphocyte count was not found to be correlated with complications in the study by Mullen (31).

Other studies have found that while normal peripheral lymphocyte count is initially maintained in protein-calorie malnutrition, the number of T cells as measured by rosette formation is decreased (33). It is believed that there is a corresponding increase in null lymphocytes which have not yet fully differentiated. A diminished T-cell-dependent immune response results from this lack of functional differentiation. Specialized T lymphocyte functions like specific proliferation, lymphokine production and release, and cell-mediated killing with a primary antigen challenge might be lost. Following the initial maintenance of a normal total peripheral lymphocyte count in protein-calorie malnutrition, a reduction in the count is found to occur (34).

A retrospective study of risk factors predictive of postoperative sepsis in 105 patients admitted for elective and emergency gastric and colonic operations by Lewis and Klein (35) reported that the development of postoperative intraabdominal abscesses and bacteremia were significantly associated with serum albumin levels below 2.7 gm/100 ml or below 3.4 gm/100 ml, preoperative lymphocyte counts below 1000/mm^3, and contaminated or dirty wounds. A prospective study was then performed to evaluate the same series of risk factors in 125 patients admitted for major abdominal and thoracic operations. Serum albumin levels, preoperative lymphocyte counts, and contaminated or dirty wounds were again found to have a highly statistically significant relation to postoperative sepsis. There was a close association between lymphocytopenia and severe hypoalbuminemia.

Lewis and Klein (35) also found risk factors to be additive. No septic complications were found in 70 patients without these risk factors. Five of eight patients with two or more risk factors developed postoperative sepsis.

As in Seltzer's study (31), Lewis and Klein also used total lymphocyte count as an indicator of immunocompetence. Both studies found a significant correlation between a decreased lymphocyte count and septic complications. The authors support their contention that total peripheral lymphocyte count is a valid test of immune function by citing the correlation between lymphocyte count and delayed cutaneous hypersensitivity reaction, as reported by Lee et al (36).

In a 1980 study by Ching et al (37) serum albumin was found to be a significant indicator of prognosis in a series of 34 critically ill surgical patients. Serum albumin levels less than 3.5 gm% were found in 31 of 34 patients at some point during their admission. The patients who survived were able to elevate their albumin levels to greater than 3.5 gm% with nutritional support. Those who died had received equivalent nutritional support but were unable to raise their albumin levels. This study is consistent with the association with poor prognosis of diminished high-priority protein pools (circulating proteins, immune function, wound healing) and the traumatic stress of surgery (10).

Preoperative identification of patients at risk for postoperative morbidity and mortality was tested by Pietsch and Meakins (38). Delayed hypersensitivity skin testing was done in 472 patients prior to major abdominal surgery. Anergic and relatively anergic (one of five antigen-positive) patients were found to have a statistically significant greater incidence of postoperative sepsis and death than the patients classed as normals.

In another study of 354 patients, Meakins and Pietsch (28) found significant correlations between anergy and decreased neutrophil chemotaxis, decreased E rosettes, and the presence of serum inhibitors of neutrophil and lymphocyte function. A study of delayed hypersensitivity by Christou and Meakins (39) demonstrated a relationship between decreased lymphocyte chemotaxis and cutaneous anergy which parallels that of decreased neutrophil chemotaxis. They postulate that anergy in surgical patients may be the result of the presence of serum inhibitors of lymphocyte chemotaxis that also inhibits neutrophil chemotaxis. No correlation with indicators of nutritional status was made in these studies.

Meakins and Pietsch (28) also found gram-negative rods and gram-positive cocci, believed to be controlled by humoral and phagocytic mechanisms, as agents in the sepsis of the anergic patients. These organisms were similarly found to be responsible for the infectious complications in the patients reviewed by Lewis and Klein (35). These studies demonstrate that although cell-mediated immunity is thought to be reflected by delayed hypersensitivity testing, a broad range of other immunologic abnormalities may also be associated with anergy and can result in decreased host resistance and increased risk of infection.

A series of 1,332 surgical patients were tested by Meakins et al (40) for delayed cutaneous hypersensitivity and compared with postoperative sepsis and mortality findings. A statistically significant higher rate of sepsis and mortality was found in patients who were anergic or relatively anergic during their hospital course. Of the 279 anergic patients, 52% had sepsis and 36% died. Of the 125 relatively anergic patients, 34% had a septic complication and 21% died. Only 7% of the 928 patients with normal skin tests had sepsis and 2% died. Interpreting the results of this study is problematic because it is not specified at what point the skin tests were performed. Patients who were anergic at any point during their hospitalization were included in the results. In addition to the immunosuppressive effects of malnutrition, malignancy and its treatment, drugs, and aging which were cited in preoperative studies, Meakins et al should have considered surgical stress, anesthesia, and postoperative infections as immunosuppressive agents in the development of anergy. The uncontrolled immunosuppressive variables in Meakins et al (40) make the choice of a therapeutic approach to anergy less specific.

Johnson et al (41) found 26% of 197 patients admitted for major general, vascular, or thoracic surgery to be anergic and 27% to be relatively anergic. The anergic patients had a significant three times greater risk of postoperative complications and a nine times greater risk of postoperative mortality than normal and relatively anergic patients. This difference remained significant when the 25 patients tested postoperatively were excluded from the analysis, thereby eliminating the potential anergy-inducing effect of surgery. The distribution of skin-test responses was found to be similar in the 50 cancer and the 147 noncancer patients. Total lymphocyte counts, neutrophil and platelet counts, total protein and serum albumin, and iron binding capacity were found not to correlate with delayed hypersensitivity testing. The results confirm Mullen's skin-test findings (31) but do not verify the predictive value of nutritional indicators such as serum albumin and transferrin. Interpretation of the results is more readily made in this study because of the author's identification and analysis of potential variables including malignancy and the timing of skin testing in the patient population reviewed.

Mullen (42) performed a more extensive study to determine a means of preoperatively identifying surgical patients at increased risk for morbidity and mortality. Nutritional assessment of 161 patients was again performed and their clinical course and outcome was followed. Of the 10 variables tested, serum albumin, serum transferrin, delayed hypersensitivity reaction, and triceps skinfold measurements were found to be the abnormal nutritional and immunologic variables which correlated with increased morbidity and mortality. A computer-based stepwise regression procedure and discriminant analysis were used to develop a formula, based upon the variables found to have prognostic significance, to determine more precisely the predicted risk of operative complications in the individual patient. The formula was then applied to a heterogenous group of 100 surgical patients to compare predicted and actual outcome of surgery. As the degree of predicted risk increased, statistically significant increase was noted in the actual incidence of death, nonseptic complications, sepsis, and major sepsis. The model classified 93% of patients who died, 92% of those with major septic complications, and 89% of those with nonseptic complications as high or intermediate risk. Of those classified as high risk, 46% developed complications, but the high-risk category included all patients with a predicted risk of greater than 50%.

This study is useful in providing an attempt at formulating a means of predicting operative risk based on indicators of nutritional and immunologic status. However, the influence of nonnutritional factors on the complications and on the variables used in the predictive model is not quantifiable in a formula. The interaction of factors such as disease process and treatment variables with nutritional status and immune function is not defined by such a technique. A predictive index of this nature needs to be considered within the clinical context to determine risk and potential therapeutic remedies.

The studies presented thus far support the relationship between criteria predictive of nutritional and immunologic status and the level of morbidity and mortality in the surgical patient. The analysis of this relationship is made complex by the multifactorial influences on surgical outcome. Moreover, it is invalid to assume that the various indicators of malnutrition will be accurate over a wide range of nutritional deficiency. This assumption presumes a linearity of relationship which, according to Habicht (43), does not exist. A recent study by Brown et al (44) failed to demonstrate any predictive value in delayed hypersensitivity testing; 28% of 244 patients had depressed skin reactions preoperatively. They did not have a significantly higher rate of sepsis or mortality than patients who had normal skin tests. Only hypoalbuminemia was found to be significantly related to an increased incidence of sepsis. Although this study is at variance with the majority of previous findings, it serves to question the relationship of malnutrition and cutaneous anergy.

Forse et al (45) were critical of the biochemical and anthropometric criteria used to assess nutritional status in studies which evaluate the relationship of nutrition to morbidity and mortality in surgical patients. Their study compared the value of body composition measurement for assessing nutritional status with biochemical and anthropometric parameters in 216 general surgical patients and morbidly obese patients. Body composition measurement uses total exchangeable sodium as a measure of extracellular mass and total exchangeable potassium as a measure of body cell mass. The sodium-potassium ratio can be used to quantitatively monitor nutritional status because of the loss of body cell mass and the associated rise in extracellular mass found in the malnourished state. They found insufficient sensitivity and specificity when the anthropometric and biochemical parameters were compared to body composition measurements. These parameters also failed to detect significant alterations in nutritional status as determined by body composition measurements. The authors conclude that anthropometric and biochemical parameters are valuable for epidemiologic surveys but are of questionable usefulness in assessing the nutritional status of the individual patient (45).

Total Parenteral Nutrition

The importance of determining the significance of the predictive criteria for operative morbidity and mortality is related to the therapeutic measures which can be used. The availability of total parenteral nutrition for use in reversing nutritionally related immune deficiencies makes more precise identification of candidates desirable. The potential technical, infectious, and metabolic complications (46–48), the prolonged hospitalization, and the increased cost argue for a discriminating use of the technique. The complexity of influences on the anergic response and immune function makes a determination of patients who will benefit from nutritional support difficult.

Studies have been performed in animal and human subjects to evaluate the effect of nutritional repletion on immunologic measurements and to establish parameters for its use. A study using the protein-depleted rat model by Law, Dudrick, and Abdou (49) demonstrated the value of protein repletion in improving the immune response previously impaired by nutritional deficiency. A comparison was made between rats protein-repleted 48 hours prior to antigenic challenge and those repleted 48 hours after antigen immunization to determine the significance of protein nutritional status on the immune recognition phase. Immune parameters tested were supranormal in those repleted 48 hours before antigen administration. Subnormal responses persisted in those repleted 48 hours after sensitization. This finding supports the conclusion that adequate nutritional intervention at the appropriate time may restore immunocompetence in the nutritionally deficient patient.

Dionigi et al (14) designed an experimental study to evaluate the ability of nutritional support to restore abnormal immunological variables under controlled experimental conditions. Sixteen dogs were studied in three groups: malnourished and TPN treated, normal controls, and malnourished controls. Immune deficiencies found in the malnourished dogs compared to the controls consisted of a significant decrease in IgG, C3, the primary immune response to sheep red blood cells, total lymphocyte count, in vitro lymphocyte response to phytohemagglutinin, and neutrophil chemotaxis. TPN for 21 days resulted in the return of IgG, IgM, and C3 to normal or supranormal levels of serum concentration. This finding is consistent with the supranormal responses found by Law (49) in the immune parameters of protein-repleted rats.

The primary immune response was also found to be more rapid after TPN treatment and neutrophil chemotactic responses improved. Peripheral lymphocyte count and the in vitro response to phytohemagglutinin did not improve significantly with TPN. This study is not strictly applicable to human patients but it allows for greater control of the variables which must be considered in the interpretation of human studies. It demonstrates the broad range of immune deficiencies found in an experimental controlled state of malnutrition and the ability of TPN to restore immune function.

A limited study to evaluate the effects of nutritional repletion in human subjects was performed by Dionigi (50) on a group of eight malnourished, nonneoplastic surgical patients. The patients had abnormally low serum levels of IgA, IgG, IgM and reduced leukocyte migration prior to TPN. All serum immunoglobulins were found to significantly increase following treatment as did leukocyte migration. In vitro tests of lymphocyte response to phytohemagglutinin stimulation showed a statistically significant improvement in ^{3}H-thymidine uptake by lymphocytes following TPN treatment. The blast transformation which occurs when lymphocytes are exposed to a nonspecific mitogen can be tested by thymidine incorporation. These results suggest a restorative influence of TPN on humoral and cellular immune function. However, the small sample size and the lack of description of the criteria used to determine malnutrition in the sample diminish the generalizability of the results.

Law et al (51) evaluated a group of 18 malnourished patients and 12 controls to determine the effects of TPN on immunocompetence. This study excluded patients with liver disease, nephrotic syndrome, protein-losing enteropathy, known malignancies, or inherited immunologic disorders. In vivo delayed hypersensitivity tests and in vitro lymphocyte phytohemagglutinin response and B cell specific pokeweed mitogen were found to be significantly impaired in the malnourished patients. Statistically significant improvement was seen in these tests following an 18-day course of TPN given to seven of the malnourished patients. There was no significant change noted in serum immunoglobulins following TPN. In vitro improvement was found in B cell specific proliferation to pokeweed mitogen. An important element of this small study is that it attempted to control for variables which might influence the interpretation of the results.

The delayed hypersensitivity response of a series of 47 malnourished cancer patients who were candidates for nutritional support was studied by Copeland et al (52). The patients were tested prior to the onset of TPN and sequentially at weekly intervals during their treatment with surgery, chemotherapy, and radiation therapy. Chemotherapy responses were noted only in patients who initially had positive skin tests (5/23) or who developed positive tests during therapy (13/23). None of the five radiation therapy patients developed or maintained positive skin tests. Only two of the six surgical patients maintained positive skin tests and had an uncomplicated recovery. Those with negative tests had a prolonged postoperative recovery or died. It is not clear from this study that nutritional support was responsible for any change in immune function. No control group was used in the study because the authors felt it would be unethical to deny the patients the benefits of nutritional support. However, malignancy and its treatment can produce anergy. The reversal of the anergic response may simply be an indication of an improvement in the disease process and not a direct consequence of the patient's nutritional status as asserted by the authors.

The problems associated with attributing causation to a finding of immune deficiency in the malnourished patient and monitoring the immune response to TPN were studied by Mullin and Kirkpatrick (53). They examined the effect of TPN on immune competency in malnourished patients with trauma, sepsis, or malignant disease. The 39 patients were grouped for comparison of their response to TPN by their degree of malnutrition, underlying trauma, sepsis, or malignancy, and skin test reactivity. The first group served as the control and had only moderate malnutrition as defined by weight loss and serum albumin levels. The second study group had trauma, sepsis, or malignancy and moderate malnutrition but were found to be immunologically competent as determined by skin test reactivity, lymphocyte count, and serum globulin levels. The third group also had trauma, sepsis or malignancy, were moderately malnourished, and were immunologically competent except for anergy. The fourth group was suffering from trauma, sepsis, or malignancy, was severely malnourished, and was immunologically impaired in all categories. No statistically significant differences were found in skin test reactivity following treatment with TPN for an average 15 ± 5 days in all groups. The only immune parameter found to improve significantly was total lymphocyte count, in group four.

This study examined conditions which are often found to overlap. They are all associated with diminished immune function as commonly measured by the delayed hypersensitivity response. The authors conclude that monitoring of the immunological value of nutritional repletion by skin test reactivity is unreliable because of these alternate anergy inducing conditions. Although this study suffers from its small size, it demonstrates the problems associated with analyzing results from the studies of nutritional repletion in immune deficiency.

Few prospective studies have been performed to objectively document the efficacy of preoperative nutritional support in reducing operative morbidity and mortality in patients with protein-calorie malnutrition. Mullen et al (54) performed a study on 145 patients who underwent a major intraabdominal or intrathoracic surgical procedure. The predictive nutritional index developed in an earlier study by Mullen (41) was used to determine if the patients identified as being at risk for operative morbidity and mortality would benefit from preoperative nutritional support. Clinical criteria and not randomization was used in deciding to initiate nutritional support because the index had not been developed at the onset of the study. The nutritional index was used for a retrospective evaluation.

A little over a third of the patients (34.5%) were treated with preoperative TPN for a minimum of seven days. The remaining 63.5% received no preoperative support but 93% of all patients were treated in the postoperative period. Of the 64 complications, 58% were septic (wound infection, urinary tract infection) or major septic (septicemia, intraabdominal abscess, pneumonia). The severity of the underlying disease in this patient population is indicated by the death of 20% of the patients studied.

Statistically significant differences in morbidity and mortality between patients who received preoperative TPN and those who did not were found. Of the pre-operatively treated group, 18% had complications and 4% died. Of the group not treated preoperatively, 38.9% had complications and 29.4% died. The greatest difference was noted in major septic complications, which were found in 4% of the TPN-treated and 21% of the nontreated. A significant difference was noted in the incidence of bacteremias, which were found in 2% of TPN-treated and 13% of nontreated patients. These disparities may reflect the immunological deficit in the nutritionally depleted patients.

The patients who received preoperative TPN may not be strictly comparable to those who did not because only clinical criteria were used in their assessment and not randomization. Analysis of the two groups, however, reveals virtually identical statistics for age, sex, underlying disease process, and nutritional status as determined by Mullen's predictive nutritional index. The index identified almost the same proportion of high-, intermediate-, and low-risk patients in both groups and the distribution of nutritional risk among the patients approximated a bell-shaped curve. No statistically significant reductions in morbidity and mortality were found in patients identified as low or intermediate risk in the treated or untreated population. The high-risk patients were found to have a significant 2.5-fold reduction in complications, a 6-fold reduction in major sepsis, and a 5-fold reduction in mortality. This study is suggestive of the importance of TPN in reducing morbidity and mortality in patients identified as nutritionally and immunologically deficient.

A study of 84 patients with gastrointestinal malignancy by Holter et al (55) evaluated the effects of TPN on postoperative complications. Patients were randomized to receive or not receive TPN, based on weight loss of 10 lbs or greater over a two-to-three-month period. TPN was given for 72 hours prior to surgery. No significant differences were found in complication rates between study groups. The failure of TPN to significantly alter the complication rate in this study may be related to its design. The 72-hour period of preoperative support may have been inadequate to reverse the deficit. The period of preoperative nutritional repletion used by Mullen (54) was at least 7 days. The use of weight loss as the only criterion for determining randomization into the study may have been inadequate as a measure of the need for nutritional support. Mullen (42) did not find weight loss to be predictive of operative morbidity and mortality and its improvement may therefore not significantly alter postoperative course.

The improved immunologic profile indicated by TPN normalized tests of immunocompetence was not found to correlate with decreased morbidity and mortality in a study by Heatley et al (56). A randomized clinical trial was performed involving 74 patients with upper-GI cancer. A 7–10 day course of parenteral nutrition was given and its effectiveness was monitored by correlation of morbidity and mortality with immune and biochemical findings. The only significant decrease in morbidity was found in wound infections. There were no significant differences in tests of immune function in either group pre or post-operatively. These results are contrary to the findings of improved hypersensitivity by Law (51) and Copeland (52). The limited benefit of decreased wound infection was judged by the authors to be an insufficient gain compared to the cost, prolonged hospitalization, and potential complications of TPN. The anergy inducing effect of malignant disease, however, may have influenced the results of this study and must be considered in interpreting its significance for patients with protein-calorie malnutrition.

Summary

The reported 50% prevalence of protein-calorie malnutrition in the hospitalized population and the major contribution of septic complications to morbidity and mortality underscore the importance of establishing predictive criteria for nutritional and immunological deficiencies. The broad range of immunological functions found to be altered by protein-calorie malnutrition needs to be correlated with morbidity and mortality to identify patients at risk. The predictive index described by Mullen (42) was formulated from the four criteria found to correlate with post-operative complications. Serum albumin, serum transferrin, delayed hypersensitivity, and triceps skinfold measurements were also determined to be related to increased complication rates in other studies, but not in all cases. Some studies also found a correlation with total lymphocyte count and postoperative sepsis. Part of the difficulty in undertaking and comparing studies of this nature is the confounding variables which may affect the interpretation of the data. The immunosuppressive potential of malignancy, infections, surgery, anesthesia, drugs, chemotherapy, radiotherapy, and age were all factors in the studies reviewed and must be considered in comparing the results and attributing significance to the findings. The delayed hypersensitivity reaction, widely used as a measurement of immune function, has been cited as being susceptible to the effects of nonnutritional factors.

The value of total parenteral nutrition in reversing the immunological deficiencies which have been correlated with increased morbidity and mortality was demonstrated in several human and animal studies. Its interpretation also suffers from the nonnutritional factors which may interfere with the outcome. The efficacy of TPN in reducing operative morbidity and mortality was shown by Mullen (42). The few other prospective studies do not support Mullen's findings. These studies are not strictly comparable, however, because of the different criteria used to define malnutrition and the uncontrolled effect of factors such as malignancy on the outcome. The potential technical, metabolic, and infectious complications, the prolonged hospitalization, and the increased cost of using TPN make a reduction in morbidity and mortality to that of the well-nourished surgical candidate a prerequisite for its clinical use. The evidence presented here lends support to the value of TPN as a method of decreasing the postoperative complications which result from nutritional deficiencies. It also demonstrates that more prospective studies of operative morbidity and mortality which use a reproducible standard of nutritional and immunological criteria for evaluation and which control for nonnutritional variables are required before recommendations for the use of TPN for this purpose can be made.

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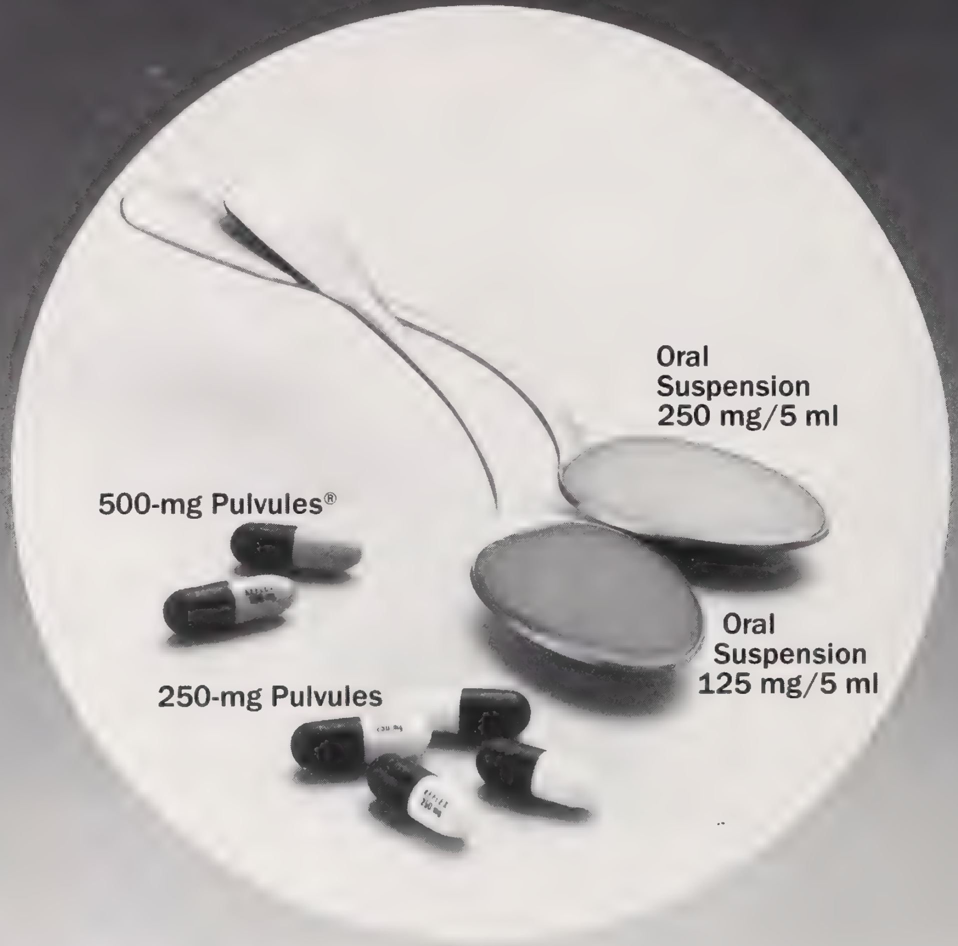
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Volume 52
Number 3
March 1985

CONTENTS

NEW FRONTIERS IN SURGICAL ONCOLOGY

Introduction *James F. Glenn, M.D.* 158

Cancer Surgery: The View from Cancer Medicine *James F. Holland, M.D.* 159

Tumor Growth Kinetics *Larry Norton, M.D.* 161

What Is Cancer Surgery? *Michail Shafir, M.D.* 165

Management of Colorectal Cancer *Arthur H. Aufses Jr., M.D.* 172

Treatment of Hepatic Metastases *Roy B. Jones, M.D.* 176

Breast Cancer: Which Operation? *Angelos E. Papatestas, M.D.* 181

Discussion 184

Thoughts on the Surgical Staging of Lymphomas *Larry Norton, M.D.* 185

Orthopedic Oncology *Herbert S. Sherry, M.D.* 189

Conservation Surgery of the Larynx *Hugh R. Biller, M.D.* 191

Tumor-Associated Immunity and Serum Blocking by Radioisotopic Leukocyte Adherence Inhibition Assay *P. H. Tsang, Ph.D., James F. Holland, M.D., and J. George Bekesi, M.D.* 193

Immune Complexes in Cancer and Preneoplastic Diseases *Michail Shafir, M.D.* 201

Prostate Cancer: Clinical Trials of Gonadotrophin-Releasing Hormone Analogs as an Alternative to Orchiectomy *Vincent Hollander, M.D., Ph.D.* 205

Summary *Michail Shafir, M.D.* 207

continued

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CONTENTS *continued*

GENERAL ARTICLES

Experimental Colitis and Colonic Cancer in the Rat *P. G. Davey, M.D., MRCP, E. E. McGuinness, B.Sc., S. Nicol, MBChB, and K. G. Wormsley, D.Sc. M.D., FRCP* 209

Cystic Islet Cell Tumor: Diagnosis and Surgical Management *David A. Loiterman, M.D., Ira S. Schwartz, M.D., and Arthur H. Aufses, Jr., M.D.* 212

Doses to Organs at Risk from Mantle Field Radiation Therapy Using 10 MV X-Rays *Ping S. Wong, M.S., Peter J. Rosemark, Ph.D., Marilyn C. Wexler, M.S., Stephen H. Greenberg, M.D., and Ronald W. Thompson, M.D., FACR* 216

Hepatocellular Carcinoma Presenting as Sphenoid Sinus Metastasis *Jenny S. Waxman, M.D., Burton Seife, M.D., and Marian Waxman, M.D.* 221

Nonmedullary Carcinoma of the Thyroid Gland in Association with Amyloid Goiter: Case Report *Alan J. Liftin, M.D.* 225

Laparoscopy for Gastrointestinal Diseases *Barry Salky, M.D., Joel Bauer, M.D., Irwin Gelernt, M.D., and Isadore Kreel, M.D.* 228

Index to Advertisers

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New Frontiers in Surgical Oncology

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New Frontiers in Surgical Oncology

From a symposium

Held November 18, 1983 at The Mount Sinai Medical Center in New York City

Sponsored by the Departments of Surgery, Obstetrics and Gynecology, and Neoplastic Diseases and The Page and William Black Post-Graduate School of Medicine of The Mount Sinai School of Medicine (CUNY) and co-sponsored by the American Cancer Society, New York City Division

Introduction

I think it fitting to reflect here on the tremendous advances that have been made in the field of cancer over the last thirty years. The articles that appear in this issue, originally presented in a very exciting day of concentration on surgical oncology, have been written by some of the people who have made major contributions toward these achievements. We at Mount Sinai are very proud of our capabilities in managing malignant diseases and in the advances in which we have taken part on a broad front—medical oncology, surgical oncology, the basic understanding of malignant disease.

In my own field of urology, I take great comfort in the fact that we have been able to reduce mortality rates from a large number of genitourinary malignancies. Testis cancer was a death warrant in young males just two decades ago, and today, with the advent of cis-platinum and other chemotherapeutic agents, we can assure survival, and indeed cure, in virtually 95% of all with testicular tumors. This is a major advance. Similar advances in the combined surgical, medical, and radiotherapeutic management of other genitourinary malignancies have not been quite as dramatic but are still extremely encouraging. Of course, the sad fact is that we have much to do in some areas; bladder cancer, for example, is still increasing in prevalence and frequency and has not come under good control.

I am sure that anyone in any discipline could recite similar advances, and yet of the three major killers, cancer is the one that is increasing in frequency. In the last 30 years, the death rate from cancer, generically, has risen from approximately 125 per 100,000 population per year to 135. Why? The reason, in part, is that the death rates from the other two major killers, heart disease and stroke, have decreased, and very clearly people will die of some diseases. Nevertheless, while we can congratulate ourselves on the progress we have made, we still face a major challenge in controlling malignant disease, because it remains the most prevalent of all the major killers.

What is the future for oncology? Obviously it lies at the cellular and subcellular level. I think that we are just at the threshold of fundamental understanding and that through molecular biology and genetic research we shall identify the causes of cancer and consequently be able to control it much more readily.

The articles in this issue will be among the steppingstones in the understanding of these fundamental principles.

JAMES F. GLENN, M.D.
President
Mount Sinai School of Medicine
Professor of Urology

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Cancer Surgery: The View from Cancer Medicine

JAMES F. HOLLAND, M.D.

The major progress already made in leukemia research, which is well known, has come about in part from thinking of cancer, when it manifests as leukemia, in terms of the number of cells involved. It is easy to count the cells in the peripheral blood, to estimate the cells in the marrow and the spleen, and to calculate the size of the leukemic population in terms of cell number. I think we must get away from the concept of "solid" tumors. Solid tumors are not solid. They are made up of tumor cells, blood, stroma, necrotic debris, inflammatory cells, edema, and immune cells. Conceptually, we would go a long way in surgical cancer research by thinking of tumors in terms of the number of cells they contain. The generic term *polycytoma* can be made much more specific by applying more detailed terms: *kilocytoma,* for tumors of 1,000 cells; *megacytoma,* for tumors of a million cells; *gigacytoma,* for tumors of a billion cells; and *teracytoma,* for tumors of a trillion cells. A kilocytoma of 1,000 cells is invisible. A megacytoma of a million cells is impalpable. A gigacytoma of one billion cells is barely detectable clinically. A teracytoma of one trillion cells weighs about a kilogram and is a massive tumor clinically. Clinical detectability comes late in the life cycle of a cancer.

Chemotherapy and Surgery. Chemotherapy has often been used for patients who are in the advanced stages of disease with metastatic cancer. If surgeons were restricted to operating only on patients with advanced disease, with all the metabolic and immunologic consequences thereof, they might well enjoy similarly limited success.

The major interaction between chemotherapy and surgery that could and should come about is illustrated in a study by Griswold, Skipper, and Schabel (Fig.). A mouse tumor implanted on day zero grew until it became palpable on about day five. The course of the tumor growth thereafter is not logarithmic but bends over toward its asymptote. Indeed, the growth is Gompertzian, which is logarithmically decelerating logarithmic growth. When the tumor reached a gram in size, Griswold, Skipper, and Schabel initiated treatment. The tumor, starting at 100% size, regressed (along line B), diminishing 90%. By clinical medical oncologic standards, the 90% regression before the tumor began to grow again would be considered impressive. But this does not reflect what truly happened. The treated tumor cells were excised and explanted at different time intervals to naive animals that served as in vivo assay systems. Shortly after administration of the drug, and reaching a maximum about two days later, there was a major oncocidal effect: not 90% but 99.999% of the tumor cells were killed by this treatment. Extremely rapid regrowth followed. The "solid" tumor represented in line B really consisted of necrotic tissue, edema, stroma, inflammatory cells, and blood, in addition to viable tumor cells. Strategies based on tumor size doubtless have prevented attempts at curative cancer treatment when the tumor was in fact very close to being cured. If the tumor mass can be reduced by surgery, we come closer to a cell population sufficiently low that chemotherapy may drive the tumor through the cure barrier.

We have used chemotherapy alone, and surgery plus chemotherapy. We are moving into the era of chemotherapy prior to surgery, followed by chemotherapy or radiotherapy.

Functions of Surgery. Three types of surgery were once used in cancer: diagnostic, curative, and palliative surgery, the palliative approach

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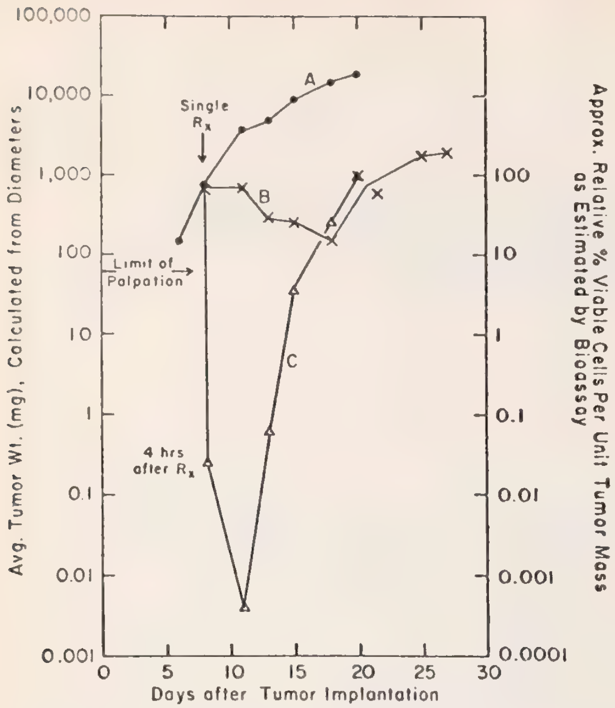

Fig. Partial regression of Pla-1 tumors following single 25-mg/kg dose of cyclophosphamide compared to tumor stem cell kill and regrowth. A, tumor mass behavior curves for the control; B, for treated group; C, tumor stem cell reduction and regrowth based on bioassays and related to untreated controls. Tumor mass behavior may underestimate tumor stem cell kill by a lot. From Griswold DP Jr, Schabel FM Jr, Wilcox WS, Simpson-Herren L, Skipper HE. Success and failure in the treatment of solid tumors: I. Effects of cyclophosphamide (NSC-26271) on primary and metastatic plasmacytoma in the hamster. Cancer Chemotherapy Rep 1968; 52 (3):345–387.

being either for improved function or for pain relief. The realm of surgery now extends to five types.

Diagnostic surgery is still critically important, as biopsy or the relatively more recent diagnostic technique, staging. There are many therapeutic approaches that depend on knowing where the tumor is. Staging laparotomy, mediastinoscopy, laparoscopy, colposcopy are all relevant surgical techniques.

Primary curative surgery is the most nearly definitive kind of cancer treatment. There is now also the entirely different, secondary curative surgery. Inoperable tumors have become resectable, leading to long-term, disease-free survival. Osteosarcoma once involved limb amputation, and a death threat in 80% of the persons affected. Now, after chemotherapeutic preparation, such excellent tumor regression can occur locally that limb-sparing resections are successful without sacrificing any of the curative impact of chemotherapy on micrometastases. Secondary curative surgery after chemotherapeutic preparation has also been reported in small-cell carcinoma of the lung. Long-term disease-free survivors have been reported after resection of localized small-cell carcinoma that has regressed after chemotherapy. Similar approaches have been made in Stage III breast cancer, in Stage III ovarian cancer, and in inoperable Wilms' tumor.

The third surgical category that is highly relevant is subcurative surgery. The use of bulk reduction in treating ovarian cancer is well established. It is probable that the principle involved in bulk reduction is applicable in other diseases, but this will only be apparent where suboptimal curative chemotherapy exists. In addition, there is subcurative procedural surgery, which is necessary for cure or for significant chemotherapeutic effect: venous access, intraventricular access to the brain, intraperitoneal access, and arterial devascularization of the liver.

The fourth category of surgery, therapeutic end staging, is critically important to assessing the results of chemotherapy. It is often possible to continue treatment or to switch drugs if a subclinical tumor remains, thus continuing efforts at cure.

Palliative surgery is the fifth category. It is my contention, and it has been for a number of years, that the advent of curative chemotherapy and the improvement in radiotherapy is going to increase the indications for cancer surgery of the first four varieties. There will be more surgery, and perhaps even more operations per patient, as we steadily progress toward curative treatments for cancer. In the transitional stage, palliative surgery will also increase, because it makes sense to improve patients' well-being during their extended life span. Eventually, one could hope for and expect palliative surgery to be largely replaced by primary and secondary curative approaches.

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Tumor Growth Kinetics

LARRY NORTON, M.D.

Cell kinetics occupies a central place in the theory and practice of oncology. The language of kinetics is frequently used in the management of the cancer patient, in medical and radiation oncology as well as in surgical oncology. Such terms as *virulent, indolent, disease-free interval, remission rate, responsive, resistant,* and *growth fraction* are examples of this common tongue. The surgical oncologist is often in a unique position to both assess and alter the growth characteristics of the tumor—to assess by observing the anatomy of internal masses with greater accuracy than is possible with external physical examination or radiographic techniques, to alter by suddenly removing large volumes of viable tumor.

The science of kinetics provides concepts for understanding the growth process of neoplasia and the means and manner in which the therapist's actions affect that process. Dr. James F. Holland, in his article, introduces an important idea from kinetics: There is a numerical association between the size or volume of a tumor and the number of tumor cells within this volume. The precise relationship between tumor size and cell number may at times be difficult to specify. Murine leukemia cells, about the size of small lymphocytes, "pack" at approximately one billion (10^9) cells per cubic centimeter. This would be the upper estimate for the number of cells in an equivalent volume of a clinical adenocarcinoma, sarcoma, or even lymphoma, both because of variations in cell size and because of the magnitude of the stromal or host-cell components of these cancers. Yet, while the actual ratio of cell number to tumor size may vary widely, the concept of cancer as a cellular process is fundamental.

Growth of Cancer Cells

It is therefore appropriate to begin this discussion by considering individual cancer cells. The increase in size of any mass can occur by four major mechanisms: swelling of cells or their accumulation of protein or lipid, as in adipose tissue; increase in interstitial matter, as in edema or fibroplasia; migration of cells into the mass, as in inflammation; true cell division, mitosis or meiosis. Meiosis occurs only in germ tissue, leaving mitotic division as the most common form of durable growth. Since the 1950s, we have known that for a cell to divide in such a manner that its entire genetic content is conserved, it must pass through four discrete steps. A G_1 cell is active in the synthesis of protein and lipid, but is also making new DNA at a slow, hardly measurable rate. Following specific enzymatic and ionic events at the cell membrane, the rate of DNA synthesis may accelerate dramatically, becoming the major metabolic activity of the cell; this is termed the S phase. As the process of gene replication nears completion, the rate of DNA synthesis falls, and a return to other metabolic events marks the G_2 period. This is followed by the actual division of the cell into two progeny during the period called the M phase. The easily recognized metaphase plate is the anatomic mark of the M phase, but the S phase is just as critical for successful cell division. Indeed, the majority of chemotherapeutic agents exert their toxic effects during the S phase.

The lengths of these four periods can be determined by sophisticated laboratory techniques using radioactive precursors of DNA, or the relationship between nuclear DNA content and cell size. In general, the G_1 phase is the most variable. Cells may remain presynthetic so long that they never undergo division; this is often called a G_0 phase. However, some cells may remain in G_2 indefinitely also. The S phase is fairly uniform in

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length, but the M phase is exceedingly so, usually lasting about one hour in many mammalian cells.

When a cell divides it can do only one of three things: It can re-enter mitosis by passing through a G_1 phase into S; it can stay in G_0; it can die. The number of cells which do not survive the mitotic process can be suprisingly large. Kineticists term these the *cell-loss fraction;* a cell-loss fraction of one means that for each two cells produced by mitosis, only one will survive. This means, of course, that the total cell number will not change, for the one surviving cell merely replaces the cell which underwent division. Cells which survive mitosis can either re-enter division and hence join the proliferative pool (P cells) or stay in G_0 or prolonged G_2 and contribute to the quiescent pool (Q cells). The ratio of P cells to the whole tumor size is the growth fraction. The rate of growth of the tumor depends upon the ~~growth fraction~~, but also upon the magnitude of the cell-loss fraction and the average length of the whole mitotic process.

We can characterize tumors by these kinetic characteristics. For example, the chronic leukemias are notable for their enormous Q cell populations. Basal cell carcinomas are known for their very large growth fractions, balanced by high cell-loss fractions. Many breast and colon adenocarcinomas have low growth fractions and considerable cell losses.

The term *cell cycle* may be misleading. Individual cells do not cycle, but rather follow a linear process, passing from birth to maturity to procreation to death. The two cells which are born of the mitosis of the parent cell are not entirely new, having much of the same cytoplasm as the parent, but neither are they merely old cells recycled. *Cycle* should be understood in its broader sense. The linear process does not go on forever for most cells, which enter a terminal Q phase after many divisions. However, some cells, called *stem cells,* or *clonogenic cells,* seem to be able to divide indefinitely, although at a slower rate than their mortal counterparts. Stem cells have the unique property of being able to replenish an entire tumor population if necessary. Therefore, cure may require the eradication of these cells, which can be a difficult task for the chemotherapist, not only because of the slow cycling time of these cells, but because most of them are quiescent. We could either recruit these cells into active proliferation and hope for a successful chemotherapeutic attack, destroy them with ionizing radiation, or remove them surgically. Indeed, the depletion of stem-cell pools may be one of the most important goals of surgical extirpation. Clearly, kinetic considerations support the concept of combined-modality cancer therapy.

Exponential Growth. Much of our understanding of cell kinetics derives from the study of experimental animal tumors in which the growth fraction remains constant over time. This leads to a pattern of growth called *exponential,* or *logarithmic.* The simplest example is a single cell with a growth fraction (by definition) of 100%. One division produces two cells. A second division produces four cells. Subsequent divisions produce eight, sixteen, thirty-two cells, and so on. The tumor doubles each cell-cycle time; the doubling time is constant.

A more realistic example is one hundred cells with a growth fraction of 41.5% (Table). For illustration, the cell-loss fraction is again assumed to be zero. After one cell division we have 59 Q cells, 41 cells to replace each of the cells in the growth fraction, and 41 new cells, for a total of 141 cells. The new growth fraction is 41.5% of 141, or about 59 cells. Therefore, after the second division, we will have 200 cells, which will again rearrange into 41.5% P cells and 58.5% Q cells. Let us follow this tumor through two more divisions. The third division produces 83 new cells, for a total of 283 cells. In the fourth division, the growth fraction is 41.5% of 283, or 117 cells. Hence, after the fourth division, there will be about 400 cells. This tumor has doubled twice over four cell divisions, and will double each two cell-cycle times.

Regardless of the magnitude of the growth fraction, as long as the growth and cell-loss fractions remain constant, the doubling time will remain constant. If we graph such a pattern on semi-logarithmic paper, it will appear to be linear. However, to the eye or hand of the clinician, the tumor will appear to be growing faster with each doubling. That is, a change from 100 cells to 200 cells will be invisible to the clinician, as will a change

TABLE

Exponential Growth of 100-Cell Tumor with 41.5% Growth Fraction and 0.% Cell-Loss Fraction

Doubling times	Growth fraction (# of cells)	Size (# of cells)
0	41	100
1	59	141
2	83	200
3	117	283
4	166	400
5	234	566
6	332	800

from 10^6 to 2×10^6 cells. Yet a change from one cubic centimeter to two cubic centimeters will be perceived as a small but significant growth. However, a change from 500 cubic centimeters to one liter will be a dramatic increase in size. Of importance, each of these four changes would, by exponential kinetics, occur over the same duration of time, one doubling time. Hence, there may be a long silent period of tumor growth below the level of clinical appreciation, for it may take many doublings for the tumor to reach the level of clinical appreciation. On the other hand, the growth of the tumor may seem explosive once large size is achieved, even though there is no increase in the actual growth rate of the tumor relative to its size, no change in the doubling time.

These two concepts—the silent period and the false appearance of explosive growth—are of immediate clinical importance. The inception of a malignant process may precede macroscopic growth by years, which helps us understand the biological behavior of such surgical diseases as colorectal and breast adenocarcinoma. Additionally, we should not always attribute an apparent increase in the growth rate of a tumor to our manipulations, surgical or chemotherapeutic, for an increase in actual growth may be entirely consistent with a stable doubling time.

Further examination of the exponential pattern of growth reveals that the time interval in which the tumor increases by any constant multiple is constant. This concept is quite straightforward and is illustrated by the example in the Table. In any one cell-cycle time, the tumor increases by a constant 41.5%. In any two cell-cycle times, it increases by 100%, as we have already seen. In any three cell-cycle times, it increases by 183%, and so on.

Treatment

How do exponential tumors respond to chemotherapy? This has been an important question in experimental oncology for several decades. Most of our important concepts in this regard are derived from the work of Howard Skipper, Frank Schabel, and their colleagues from the Southern Research Institute. In their studies of murine leukemia, these authors discovered that exponentially growing tumors often regress exponentially in response to chemotherapy doses of equal intensity, spaced regularly in time. We have already seen that exponential growth means that if the tumor grows by, say, 41.5% in a certain unit of time, it will always grow by 41.5% over that unit of time, regardless of its starting size. To choose another example, say a tumor increases by a factor of ten over a month (from 1 cc to 10 cc in volume). If the tumor is measured at 100 cc at a certain point in time, it will be ten times larger, 1,000 cc, a month later, and ten times larger still, 10,000 cc, a month after that.

This same pattern applies to the regression of an exponential tumor in response to therapy. If the tumor is 1,000 cc at the start of treatment and one month of chemotherapy shrinks the tumor to 100 cc, then the tumor has regressed by a factor of ten. This is called a one-logarithm change, from 10^3 cc to 10^2 cc. If the same tumor is observed at a size of 10 cc (10^1), a month's worth of the same chemotherapy will reduce the tumor by one log to 1 cc (10^0).

This observation has been one of the most powerful in chemotherapeutics, and has been used to plan durations of treatment, intensity of treatment, and combinations of agents, each capable of producing a certain log-kill. It clearly explains the clinical observation that the actual cell-kill produced by an agent can be most gratifying on the first exposure. That is, the tumor changed by 900 cc with the first dose of drug, for a total cell kill of perhaps 9×10^{11} cells. The reduction from 10 cc to 1 cc is a constant log-kill of one, but only kills 9 cc or 9×10^9 cells. We indeed often observe that tumors regress most rapidly when we first start treating them, and less rapidly with subsequent treatments. While we often attribute this phenomenon to biochemical resistance to our drugs, exponential kinetics alone may be a sufficient explanation in many cases.

Gompertzian Deviations from Exponential Growth. The real-life situation is perhaps slightly more complicated than all of this, for unlike the case with murine leukemia, many (or most) human tumors deviate systematically from exponential growth. Discussions of this phenomenon date from the very early days of this century, but the definitive work was provided by Anna Laird in the early 1960s. She demonstrated that the curve first used by Benjamin Gompertz in 1825 for actuarial tables applied as well to the growth of cancers and even normal organs. This curve starts off exponentially but shows progressive slowing from the exponential pattern as the tumor gets larger. Eventually, the growth rate slows sufficiently that a plateau phase is reached, with no further growth. Common examples in which this pattern is intuitively obvious are colon cancers, renal-cell carcinoma, some postmenopausal breast cancers, and the indolent lymphomas. We have already mentioned that three factors influence the growth rate of a tumor: growth fraction, cell generation time, and the cell-loss fraction. The major cause of slowing growth in the Gompertzian pattern is a systematic decline in the growth fraction over time. Very large tumors, high on their Gompertzian curves, may have very low growth fractions. This is of major concern to the chemotherapist who depends upon dividing cells for the cytotoxic effect of drugs. If the medical oncologist must treat a low-growth-fraction tumor with mitotoxic agents, the population is relatively protected by a significant component of nonmitotic cells. Hence the efforts would be doomed to failure.

Tumor Resection. The good news is that it seems possible to alter this situation by changing the kinetics of the tumor, forcing it to act like a smaller tumor, earlier on its Gompertzian curve. We do this by resecting a sufficient volume of tumor that the residual mass will start to grow with an increased growth fraction. Experimentally, this has been shown by Linda Simpson-Herren, Bernard Fisher, and others, who partially resected animal tumors to demonstrate an increased growth fraction of residual foci. The value of this approach has two important qualifiers. One must resect a significant percentage of the tumor to create an important increase in growth fraction. Also, the increased growth fraction can often repopulate the tumor rapidly, so effective chemotherapy must follow effective surgery quickly to achieve meaningful synergy. Hence, if adjuvant chemotherapy following mastecomy for breast cancer is delayed too long, it may not be beneficial. This has been demonstrated in several clinical trials.

Debulking is the most rapid, most effective way to put more cells at risk for cytotoxic damage by drugs. The surgeon is the best applied cytokineticist in cancer therapeutics. But debulking has to be as complete as possible to be useful.

Surgical resection is important for another kinetic reason as well. It has been shown by Lloyd Law, based on earlier bacteriological work by Delbruck and Luria, that one mechanism for the development of biochemical resistance to drugs is the mutation of individual cancer cells. The relationship between tumor growth and the probability that no cell has yet mutated to drug resistance is based on a mathematical model in which each cell at division has a certain probability of generating drug-resistant offspring. The probability of no instances of this mutation is therefore related to the cumulative total number of mitoses in the tumor. This model extends that popularized by James Goldie and Andrew Coldman to cases of Gompertzian growth and cases of significant cell loss. If a tumor has a high rate of cell loss (as in colorectal carcinoma), many mitoses are needed to make up for the host cells. The biggest changes in the probability of there being no resistant cells occur during the rapid growth of the tumor in the middle portion of Gompertzian growth. The small tumor, early on the Gompertzian curve, has a high growth fraction but many fewer cells in total; therefore, the number of mitoses is smaller, and the probability of new mutations is small. Thus, curative chemotherapy may depend on keeping the tumor as small as possible, which may be accomplished initially by surgical debulking. The surgeon may, therefore, not only provide the medical oncologist with a tumor with a high fraction of target cells but may help limit the emergence of biochemical resistance. It is essential for the chemotherapist to begin work as soon as possible after the surgery, so that no further mutations can occur. It may even be desirable to have chemotherapy "on-board" when the operation takes place, an exciting possibility for future research.

Conclusion

Cell kinetics is not an esoteric topic for the isolated laboratory. All clinicians are kineticists. When we talk of preclinical cancer, rapid or indolent growth, remissions complete or partial, cure or relapse, disease-free interval, or surgical stage, we are speaking in kinetic terms. Cell kineticists and clinicians must continue to develop and share their common language, interests, and goals, for the good of the science and of all of our patients.

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What Is Cancer Surgery?

Michail Shafir, M.D.

My purpose here is to try to explain briefly and give a few examples of the complex role of the surgeon in oncology. As Dr. Glenn and Dr. Holland have strongly emphasized in their papers, the progress in treating cancer in the last few decades has not come via a single technique pushed to its limits, but rather via a multidisciplinary approach to treating different cancers in a predetermined fashion from time zero to the ultimate goal. In this effort, the surgeon's role has to be very clearly defined. Any surgeon or surgical subspecialist will be treating cancer patients and will have different responsibilities at different moments. Surgery can be the primary treatment. It can be an adjuvant treatment. It can be supportive, while the patient is being treated by other modalities; and it can be palliative.

The definitive treatment may be purely surgical, as is often the case with skin cancers. And, as we shall see in a few examples, selecting an appropriate procedure and performing it correctly is absolutely essential—in all cancer surgery. But the treatment does not always have to be done by a surgical oncologist. Actually, most cancer surgery is done in community hospitals by general surgeons or by otolaryngologists, gynecologists, urologists, and others; the important thing is that the treatment be appropriately planned from the very beginning and that the local therapy be appropriately conducted.

When we are dealing with particular tumors, for instance Burkitt's lymphoma or ovarian cancer, the treatment is always, and from the very beginning, a combined approach. Each specialist's role has to be very clearly defined. Similarly, combined treatments may be used for metastatic disease. Until not so long ago, a patient who had metastatic disease would be essentially written off. We now conceive things somewhat differently. As Dr. Norton notes, very often a patient who has metastatic disease that is slowly growing, that has a slow doubling time, and that is fairly localized in one area can be surgically treated by debulking the tumor so that another modality can take over and prolong the patient's life in a meaningful way.

We have surgery for palliation and—very important—we also have surgery for reconstruction and rehabilitation. I shall give a few examples of patients who have been operated on at the end stage of their disease, and who have achieved both palliation and rehabilitation.

Surgery as the Primary Treatment

A patient with a small basal-cell carcinoma of the skin (Fig. 1) will most probably consult a dermatologist for a first opinion. An adequate oncological treatment for this patient will be a limited, fairly narrow resection, which, in this case constitutes "radical" surgical treatment. The chances of the condition being cured are in the order of 98% to 99%.

On the other hand, a dermatologist may see a small superficial melanoma. This will look different from the carcinoma, and may have areas of pigmentation and of discoloration, also, melanomas grow in a quite different fashion from basal-cell carcinomas (growing vertically and horizontally and extending much further out than the visible lesion at the epidermis). Resection of a melanoma has to be much more extensive, much wider, than resection of a basal-cell carcinoma. A small local resection with a narrow margin is not adequate.

Selecting the appropriate type of resection is a daily problem in dermatologic and general-surgery practice. It is very important to diagnose

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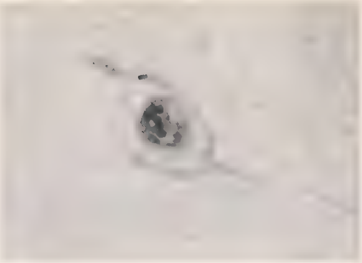


Fig. 1. Basal cell carcinoma of skin.

skin lesions properly and to treat them accordingly.

Melanoma and Lymph Nodes. With a melanoma, of course, there is always the question of what to do with the lymph nodes, for the disease frequently extends to the regional lymph nodes before metastasizing. For years, debate has been going on about what to do with these nodes—when to dissect, when not to dissect, whether to do monobloc immense excisions or much more limited excisions. There is not much discussion with respect to patients who have palpable nodes, in the absence of widespread metastatic disease: A lymph node dissection will be performed both as a curative attempt and for comfort and palliation, to keep these nodes from growing and breaking through the skin. The question arises mainly with respect to patients who have a high risk of nodal involvement and no palpable nodes.

How has this problem been approached? In one retrospective study of patients with Clark's levels IV and V of invasion by the primary melanoma, without palpable nodes, two approaches were compared: wide local excision alone versus wide local excision plus lymph node dissection. In this particular study, the survival of patients who had only the wide local excisions was much shorter than the survival of those who had the wide local excision plus lymph node dissection.

So, if one were to base the therapeutic decision upon this study, one would say definitely that all patients with levels IV and V should have lymh node dissection in addition to the excision. But we all know the drawbacks of retrospective studies in which we don't know why patient X did get a dissection, while a similar patient, Y, did not. Was it because patient Y was much sicker than patient X? Was it because patient Y had paramount medical problems that did not allow extensive surgery? Comparisons under these circumstances are difficult to interpret. This is to emphasize the absolute need for randomized studies.

Addressing this question particularly, the World Health Organization, with the participation of multiple institutions, did such a randomized study. Every Clark level and every thickness of melanoma, with no palpable nodes, was represented. Half of the patients got an elective lymph node dissection and the other half did not. In 553 cases, in a perfectly rigorous statistical study, there seems to be absolutely no difference in survival between the two groups. The conclusion from this, obviously, would be that in a properly conducted study, if one does not do a lymph node dissection, the chances of survival are not diminished. The only caution one has to observe is that there must be excellent follow-up, as there was in this study. Almost no patients were lost to follow-up, and when in any of these patients, a lymph node appeared that was clinically suspicious, a lymph node dissection was performed. Interestingly enough, the results held true for every one of Clark's and of Breslow's categories.

Multidisciplinary Treatment

A multidisciplinary approach can really improve the outlook for a patient tremendously. One example is a man who, at the age of 20, had an enormous tumor of the thigh (Fig. 2). He was originally treated at another institution. The tumor was biopsied through a long incision. At surgery, the femoral vein was found to go straight through the tumor, and during the biopsy, the femoral vein was entered and ligated. The tumor turned

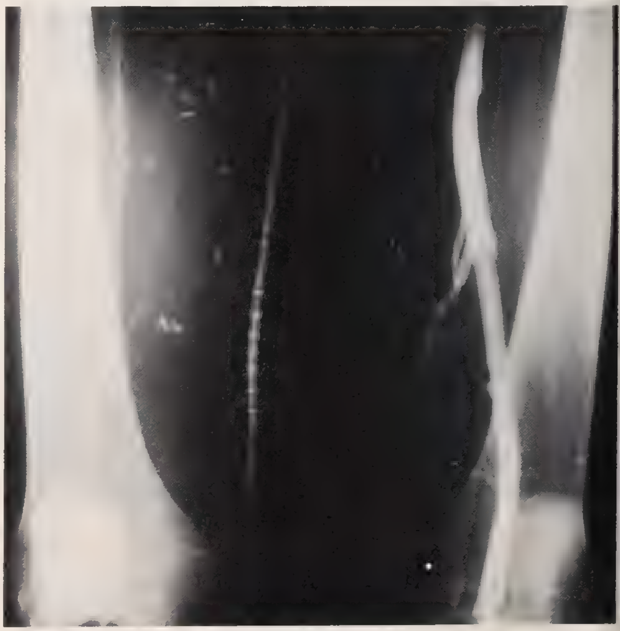


Fig. 2.

out to be a soft-tissue Ewing's sarcoma. The patient had normal preoperative chest x-ray, but as he was recovering from surgery, he developed a cough and was found to have multiple defects in the lung, interpreted as tumor emboli resulting from the entering of the femoral vein.

At this point, the patient was referred to The Mount Sinai Hospital. By combining different modalities of treatment, our success, we think, was tremendous. We ligated the inferior vena cava, as a first step, to prevent any further embolization; we radiated his thigh, encompassing the entire palpable tumor, and initiated chemotherapy. We then operated on the residual tumor and irradiated both lungs. We continued chemotherapy. Three years after treatment, the man has some muscle impairment and a scar that does not look very pretty (Fig. 3). But he is snow-skiing and water-skiing and just took a job in which he has to walk considerable distances. I think that a patient like this, approached in an old-fashioned way—only with palliative radiotherapy or only with surgery (probably amputative surgery, at the time)—would most certainly not have achieved the result that was obtained here.

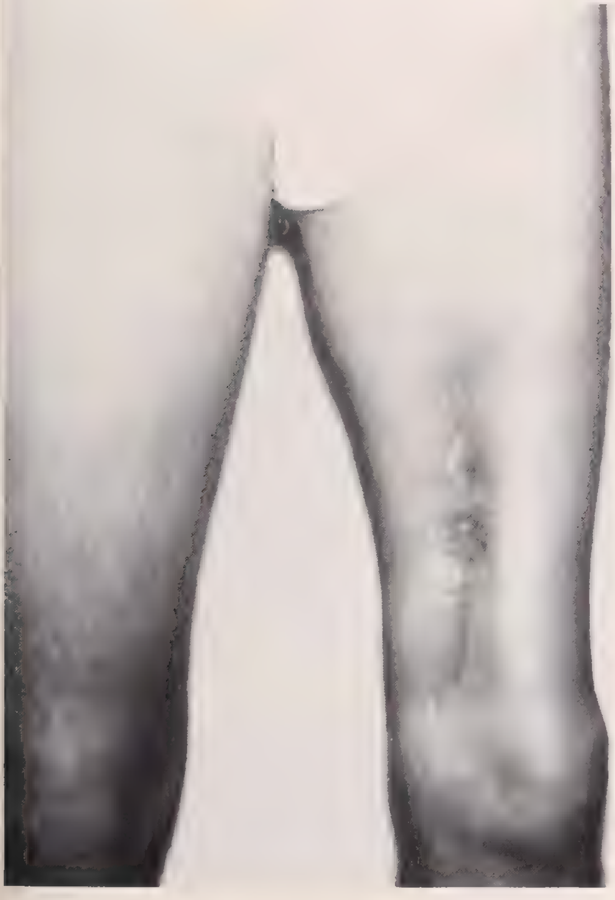


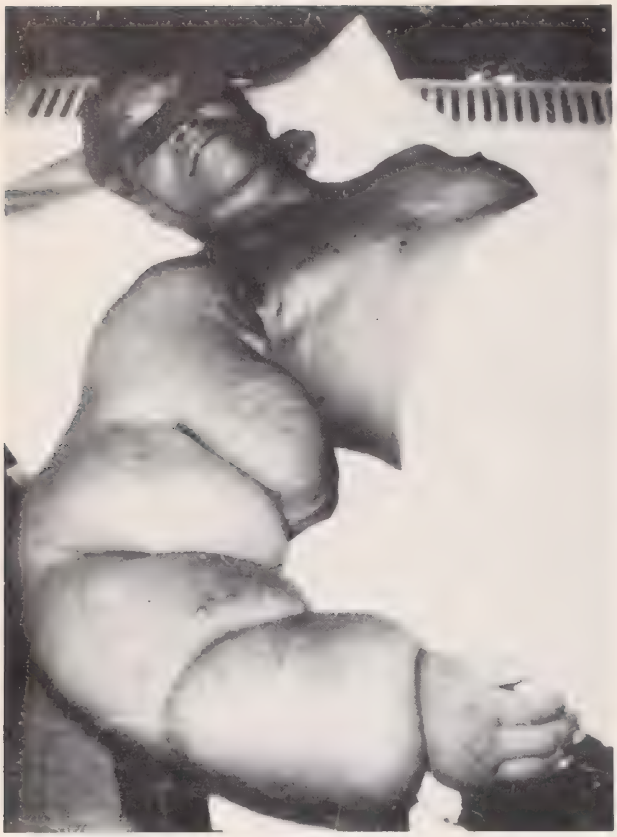
Fig. 3.

Surgery Relating to Complications

Lymphedema. We also, as surgeons, are called upon to treat the complications of cancer treatments. For instance, one of our patients is a woman, who, about ten years ago, had a radical mastectomy and postoperative radiotherapy for positive nodes in the axilla. She slowly developed very progressive lymphedema (Fig. 4). She was treated with different physiotherapeutic approaches: Jobst intermittent compression pump, elevation, exercises, and so on. The lymphedema got progressively worse. She developed a tremendous kyphosis and was completely disabled. One day, a small lesion appeared on the edematous forearm, and then one next to it. It was thought that this was lymphangiosarcoma developing in the longstanding lymphedema, and that perhaps an amputation should be considered. But the nodules, on biopsy, were not malignant, just lymphatic ectatic areas, so we operated and removed the entire fat and subcutaneous tissues, stripping down to the fascia. One month after surgery, after extensive grafts, her arm looked perfectly viable. She still had the edema in her hand, where we did not resect because of the loss of function it would have entailed; this woman can now live normally again. She can write and she can do all her normal housework. Her arm is far from esthetic perfection, but it is much better than before (Fig. 5). So here we have an example of how a complication of cancer was successfully treated with rehabilitative and plastic surgery.

Recurrence of Rectal Cancer. We also perform surgery to prevent complications of treatment. We know, for instance, that after anterior resections or after abdominal perineal resections about half the recurrences of rectal cancer occur in the pelvis. We also know from ongoing studies that a combination of treatments for rectal cancer improves the outlook considerably. In a study in which patients with rectal cancers were randomized postoperatively and received different treatments, best disease-free survival is in the group that received postoperative radiotherapy and chemotherapy.

However, when we perform an abdominal perineal resection, loops of the small bowel can fall all the way down to the bottom of the pelvis, which limits the dose of radiation the radiotherapist can effectively give, because of the tremen-



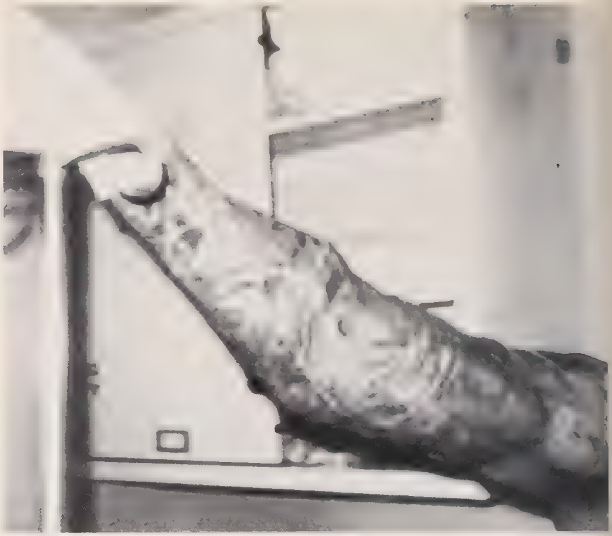


Fig. 4. **Left.**

Fig. 5. **Right.**

dous risk of fistulization and radiation enteritis. So what can we as surgeons do to facilitate this combined approach? In high-risk patients—those who have bulky, penetrating tumors of the rectum and those who have obvious lymph nodes at the time of the resection—we can pick up the peritoneum covering the bladder and tack it up to the promontorium, creating an empty space behind the bladder into which the intestine cannot penetrate. When this is not possible, we have used a Marlex mesh sling, hanging from the promontorium all around the perimeter of the pelvis, again preventing the small bowel from falling into the pelvis and allowing the radiotherapist to give a much higher dose of radiation. In a small-bowel series done in one of these patients postoperatively, we can see that his pelvis is essentially empty of small bowel (Fig. 6).

Surgery for Diagnosis

Liver Metastasis. Surgeons are also called in for diagnostic work with cancer patients. For instance, a patient may be suspected of having liver metastasis; it is crucial to know if this is so because the best choice of treatments depends on the presence or absence of liver metastasis. The difficulty is that when the liver is biopsied percutaneously, without sonographic guidance, about half of the patients with negative biopsies do have metastasis. A way to overcome this problem is by laparoscopy, which can often be done under local anesthesia or very short-acting general anesthesia. Tiny metastases, which can be entirely missed on the liver scan and on the percutaneous biopsy, can be very effectively biopsied at the time of laparoscopy (Fig. 7). Again, when the lesions are very superficial, they can be biopsied at the edge of the liver and the diagnosis established properly. Similarly, laparoscopy is

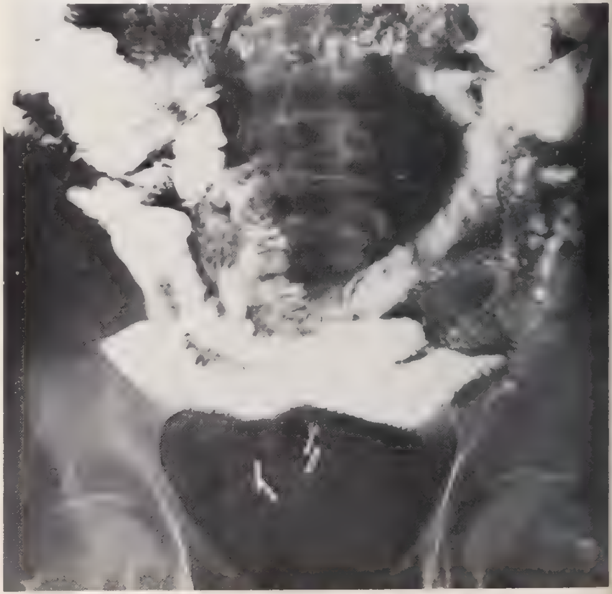


Fig. 6.

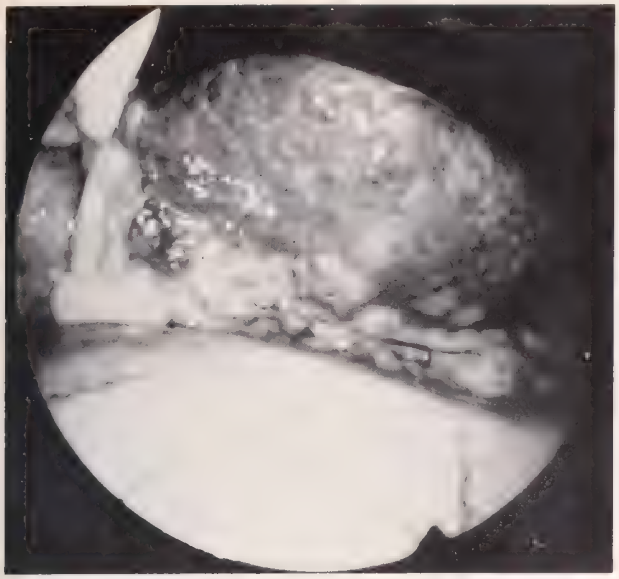


Fig. 7.

useful in diagnosing peritoneal carcinomatosis, which may not be obvious in many patients, especially if they are obese, the presence of ascites is difficult to ascertain, a tap is inconclusive, or the cytology is not entirely clear. Laparoscopy can solve the problem, for we can thus see these tiny lesions, biopsy them, and assess the extent of the disease immediately.

Surgical Supportive Treatment

Catheters in Chemotherapy. There are other ways in which surgical and chemotherapeutic techniques may be associated. One of them, discussed in detail by Dr. Roy Jones, is in intraperitoneal chemotherapy through a peritoneal dialysis catheter. A Tenckhoff catheter is placed intraperitoneally; Gastrografin diffuses in the entire peritoneal cavity (Fig. 8). In certain circumstances (carcinomatosis with small tumor bulk and/or liver metastasis), this seems to be an interesting modality of treatment.

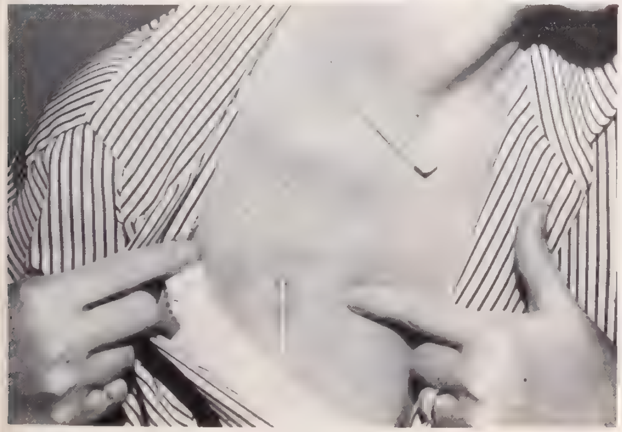


Fig. 9.

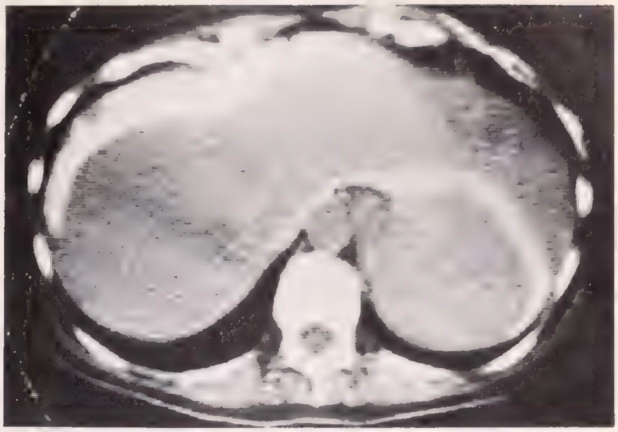


Fig. 8.

Broviac and Hickman Catheters. How does a surgeon contribute to the supportive treatment of patients who will need chemotherapy or long-term intravenous nutrition and in whom venous access is a serious problem? In the past few years, several different techniques of access have been developed. We have found that the most satisfactory are the Broviac and Hickman catheters. These are easily introduced, under local anesthesia, into an external jugular, cephalic, or internal jugular vein; we can put one or two catheters into the atrium or the superior vena cava and simultaneously have a means of drawing blood, a means of hyperalimentation when necessary, and a means of administering chemotherapeutic agents and antibiotics. We have found that the comfort and ease of care of the patient has been dramatically changed since the advent of these catheters. We have placed several hundreds of these catheters. When in place, they are unobtrusive (Fig. 9); the catheter comes out of only one small area; the patient can coil the catheter around when it is not in use, put on a T shirt, and nothing is visible at all.

We have used both the Broviac and the Hickman catheter for all kinds of different malignancies. The catheters are extremely useful in patients with hematological malignancies, in whom we place them at the beginning of treatment (before the patient has been stuck many times and is full of ecchymoses and hematomas) and when no venous access has been available at the time of severe bone marrow depression. We evaluated 182 catheter placements, and found only seven patients who had been infected, only three of

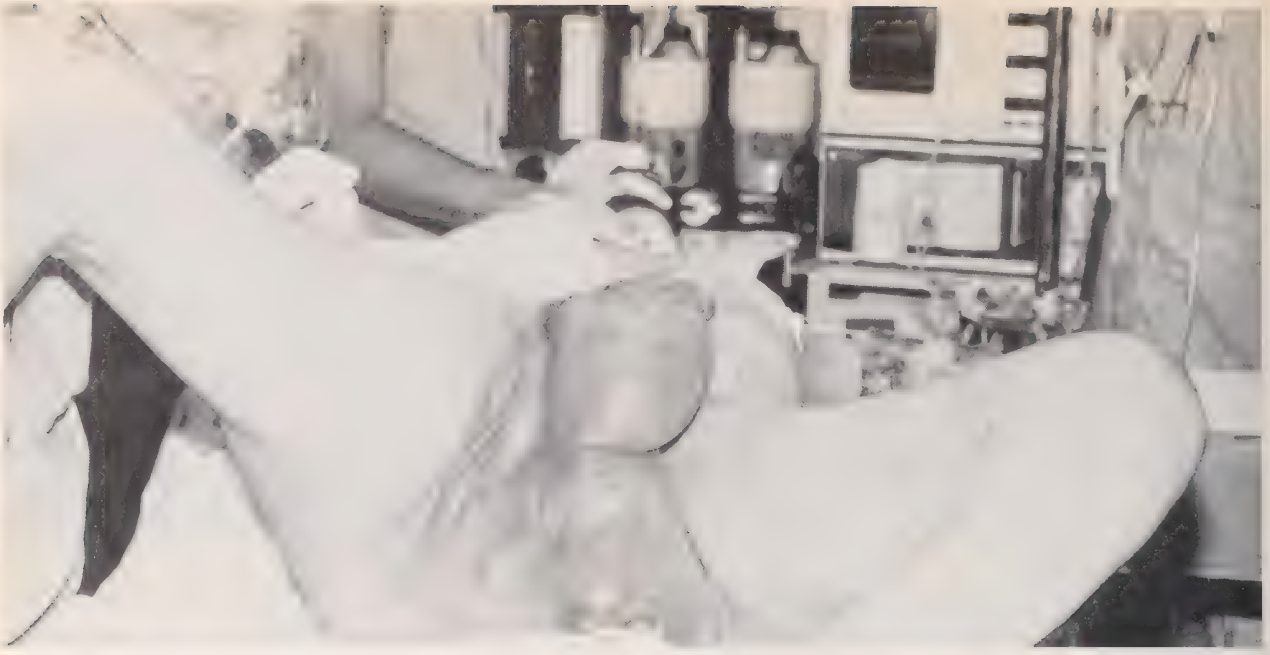


Fig. 11.

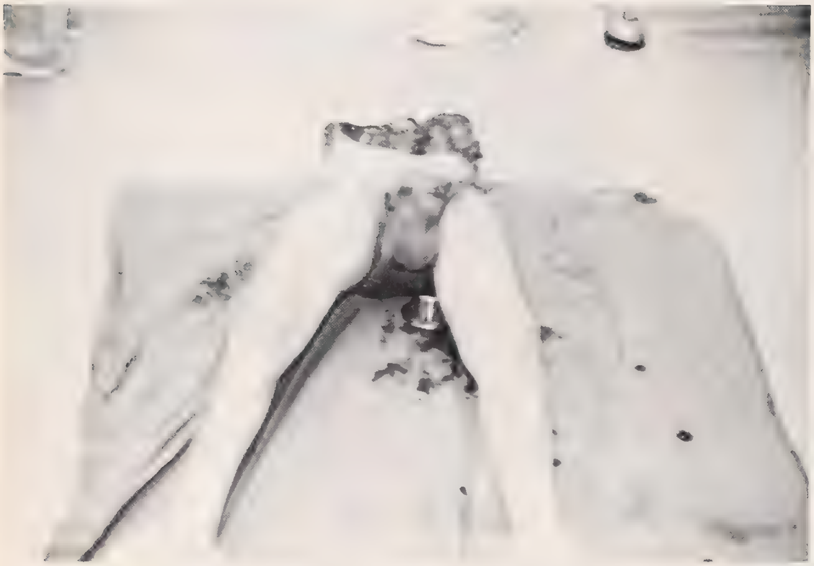


Fig. 12.

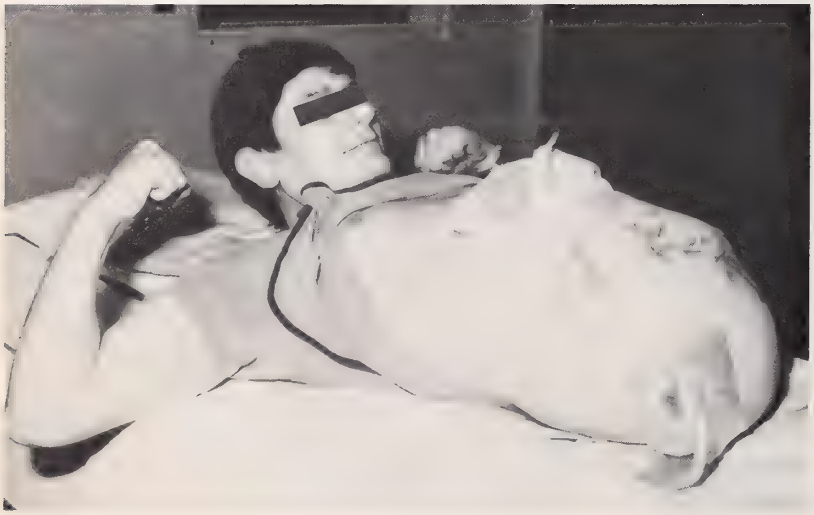


Fig. 13.

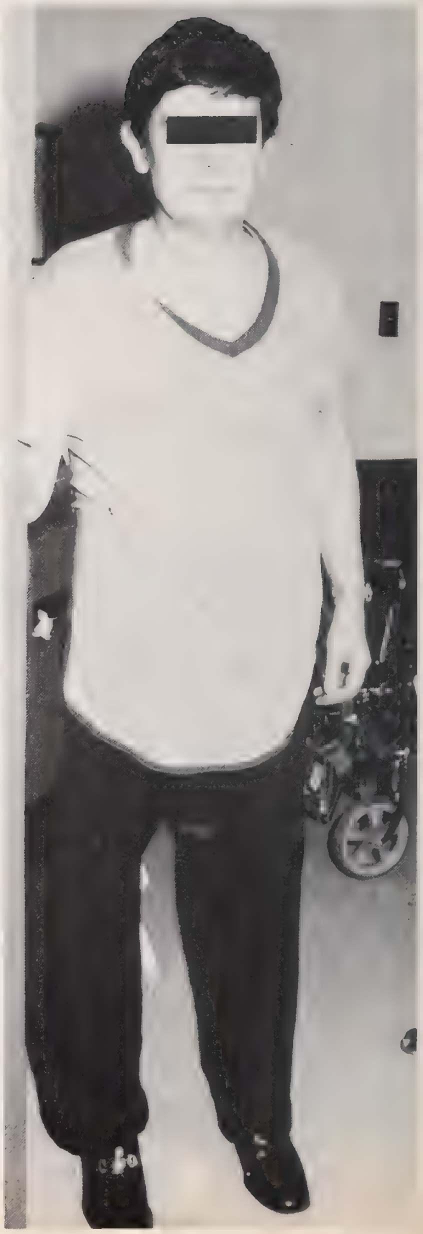


Fig. 14.

whom required removal of the catheter. We have had two significant hematomas of the operative site in patients who were thrombocytopenic at the time of the insertion. (We gave platelets immediately prior to and during insertion; nevertheless, the patients developed significant hematomas.) We have encountered seven instances of mechanical problems—catheters being sheared or punctured or broken.

"Salvage" Surgery

"Salvage" surgery is an extremely difficult subject to discuss. I do refer here to the patient who, after having multiple treatments of different varieties, has a tumor that is growing locally or locoregionally and for whom no therapy other than drastic surgery can reasonably be offered. So the patient is presented again to the surgeon. Can the surgeon do anything? We see this mainly in tumors of the extremities, the retroperitoneum, and the pelvis.

For instance, a 72-year-old woman with a repeatedly recurrent liposarcoma of the upper thigh required hip disarticulation. That woman, at age 72, is rehabilitated and is walking on a prosthesis (Fig. 10).

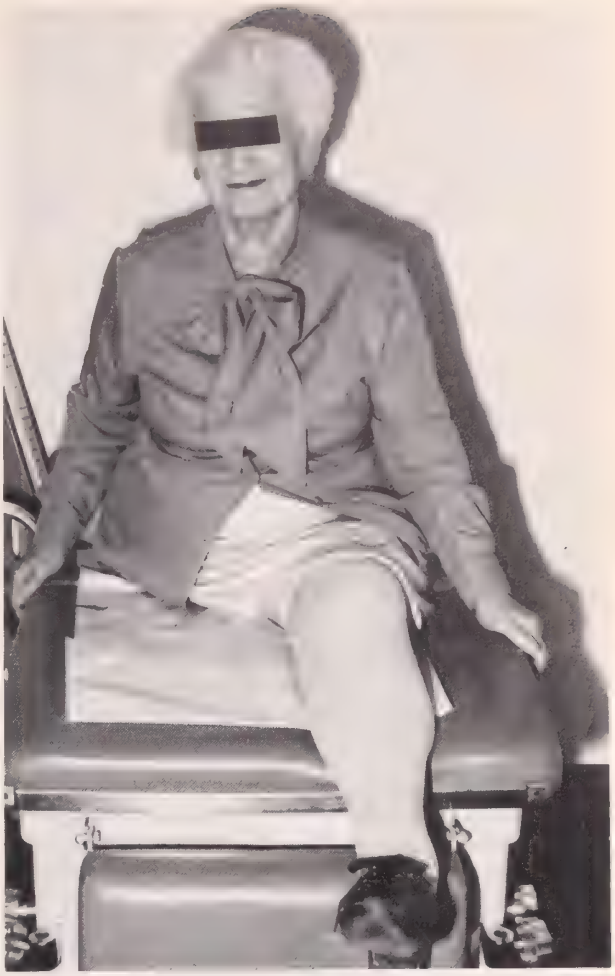

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Fig. 10.

But our most dramatic case was a man, 44 years old, who had a recurrent chondrosarcoma occupying the entire pelvis, with edema of the thighs and fistulization of the lesion through the perineum, and with involvement of the scrotum and the penis (Fig. 11). The tumor had already obstructed his rectum and had required a transverse colostomy; it had obstructed his bladder outlet, requiring a suprapubic cystostomy. The patient was in tremendous pain but perfectly lucid and grabbing at straws to live longer.

This is an example of what salvage surgery can do. We removed his tumor by cutting him in half (Figs. 12, 13) because that was the only thing that surgically could be done. In spite of this tremendous mutilation, the patient recovered well. He put a prosthesis on and at the end of six months, he could stand on his prosthesis, sit in a wheelchair, drive a van that was specially designed for him, and go back to work as a computer analyst (Fig. 14). He died two years after this hemicorporectomy, of disseminated disease, essentially of respiratory failure; but the disease had also recurred in the abdomen.

The point I want to make with the story of this patient is that in some instances, when necessary and when strictly indicated, one can perform mutilating surgery that will achieve the patient's goal. This man wanted to live a little longer to see his children grow a little more. In spite of extensive mutilation, rehabilitation is possible, and salvage procedures become a viable alternative.

This overview of surgical oncology emphasizes the broad spectrum of procedures the cancer surgeon is exposed to.

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Management of Colorectal Cancer

ARTHUR H. AUFSES JR., M.D.

Because I believe that surgery plays only a very small part in the management of any malignancy, I would like to traverse a wider range of current thinking on the management of colorectal cancer than merely talking about different ways of removing rectal tumors.

Incidence and Risk Groups

Colorectal cancer represents 14% of all malignancies in males and 15% of all malignancies in females. Colorectal cancer has been increasing in the United States by 10% per year. It is still continuing to increase, but the American Cancer Society estimated that in 1983 there would be 87,000 new cases of colon cancer and 39,000 new cases of carcinoma of the rectum. It may therefore be that the incidence is starting to decrease, or the rate of climb is starting to decrease.

What is quite clear, however, is that colorectal cancer is slowly moving around to the right side; the percentage of right-sided cancers in the colorectal arena is increasing at the expense of rectal cancer. It may very well be that the reason why the rate of climb of rectal cancer is decreasing is because of the "war" on adenomas of the rectum. There seems to be fairly good evidence that routine sigmoidoscopy with removal of every early adenoma may decrease the incidence of rectal cancer. Most people in the field believe that almost all colorectal cancers arise from preexisting adenomas. Specifically, the villous adenoma is the most important, although cancers do arise from tubular adenomas and from tubulovillous adenomas. The war on the adenoma may well have something to do with cutting down the incidence of rectal cancer.

Unfortunately, despite the modern advances in patient management and surgery, there has been essentially no change in the death rate from colon cancer per 100,000 population in the past 30 to 40 years in males; and although in females there does appear to be a decline in the death rate from this cancer, it remains a major disease.

Current thought is that over 75% and possibly up to 90% of all cancer is environmentally induced. There appears to be little doubt that environmental factors that are related to the Western diet influence the development of colorectal cancer.

On the other hand, we are now well aware of the fact that familial patterns play an important role. I believe it is important for us to look at the high-risk groups, because proper surveillance of those patients at greater risk will prevent disease, and that is certainly better than trying to cure it once it exists.

A major high-risk group are those families with polyp syndromes. Familial polyposis affects one in 8,500 births. These patients who have an autosomal dominant gene for this condition are patients with well over 100 polyps. The polyps begin to appear at any age from 15 years up to 45 years. If untreated, all of these patients will develop cancer of the colon or rectum by the time they are 60 years and will die of the disease. It therefore represents a true public health problem. Other syndromes have a lesser incidence—except recessive adenomatous polyposis. This is the group of patients that we see most often. These patients have between 5 and 25 adenomatous polyps. This syndrome affects about 9% of the American population, a group that is therefore most important in the genesis of colorectal cancer.

There are also many high-risk groups who do not have polyp syndromes. They do not make large numbers of polyps but develop cancer nevertheless. There are cancer families, and specific colon cancer families. There are specific gastrocolonic cancer families, and we are aware of the relationship between breast and colon cancer in

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the female patient. Then, finally, we know that patients with ulcerative colitis and Crohn's disease (the inflammatory bowel diseases) are at risk for the development of cancer. Recent reports also indicate that the female who has had previous abdominal or pelvic irradiation is also at increased risk for the development of rectosigmoid and rectal cancer. There is a significant lag period between the development of inflammatory bowel disease or the date of radiation and the development of cancer. The risk for cancer starts at about 8 years for ulcerative colitis and possibly 20 years for Crohn's disease, and is about 10 years for pelvic irradiation. These patients should be under surveillance for the development of colorectal tumors.

In ulcerative colitis, at the end of 25 or 30 years, one-third of the population at risk will have developed or will already have rectal cancer. Lee and Truelove have stated that the most important risk factors were total colonic involvement and the number of years at risk. Therefore surveillance programs for the development of cancer should begin at about the eighth year. (Surveillance programs are discussed below.) Crohn's disease entails an increased risk for both small-bowel cancer and colonic cancer. About one-third of the small-bowel cancers have occurred in segments of bowel that have been excluded by previous surgery. The incidence of colorectal cancer in Crohn's disease is six times that of the general population. These tumors are often multiple and may arise in areas of the colon not affected by Crohn's disease. These cancers also have a tendency to occur at the sites of fistulae and strictures produced by the inflammatory bowel disease.

A major problem that persists to this day is that the majority of patients with colorectal cancer are already at an advanced stage of the disease when diagnosed. Localized disease is a colorectal cancer limited to the bowel wall. At this time only half of patients have localized disease at diagnosis, the other half having either lymph node or distant metastatic involvement. This represents a major problem that can be in part attributed to the patients who do not seek advice when they have rectal bleeding. Unfortunately however, delay in diagnosis is frequently the fault of the physician who does not perform routine rectal examination or perform routine stool examination for blood.

Management

To discuss the specific management of rectal cancer, we must first define our terms. In the Dukes' pathological classification of colorectal cancer, an A lesion was confined to the wall of the bowel, a B lesion extended beyond the wall into the pericolonic fat, and a C lesion had metastatic disease. This classification has been modified a number of times. We at Mount Sinai have adopted a classification conforming to that of the Gastrointestinal Tumor Study Group (GITSG), which we have been part of for some time. In this classification an A lesion is limited to the mucosa, a B1 lesion involves the bowel wall but does not extend to the serosa, a B2 lesion involves the serosa and/or extends into the pericolonic tract. A C1 lesion is metastatic to lymph nodes irrespective of the depth of wall involvement but there are fewer than four lymph nodes involved. A C2 lesion has more than four involved lymph nodes. A D lesion represents any degree of local disease with distant metastasis.

There has been a significant change over the last 10 years in the management of rectal cancer. Anatomically the rectal valves divide the rectum into lower, middle, and upper segments. These valves are located approximately 5, 10, and 15 cm from the dentate line as measured sigmoidoscopically. The lower rectum therefore is that segment from 0 to 5 cm from the dentate line, the middle rectum from 6 to 10 cm, and the upper rectum 11 cm to the rectosigmoid junction.

A note of warning should be sounded here: colonoscopists measure the lesion as they see it during withdrawal of the scope. This is usually noted as being higher than the surgeon sees the lesion using a rigid sigmoidoscope and approaching the lesion from below. In other words, if a colonoscopist locates the lower level of a lesion at, say, 12 cm, it will actually be about 9 to 10 cm on sigmoidoscopy. This can make a difference in how the patient is approached in discussing various procedures.

Lesions above 10 cm can all be treated by anterior resection; that is, a resection which anastomoses serosalized or intraperitoneal bowel above to the deperitonealized rectum below. In former years all lesions below 5 cm were treated by abdominoperineal resection. However, in recent years newer modalities of treatment for certain lesions in this area have taken precedence and these are discussed below. A major change has also occurred in the management of the lesions of the midrectum. Recent reports indicate that similar results may be obtained in this area (6–10 cm) by the use of either abdominoperineal resection with permanent colostomy or low anterior resection. As a consequence, more and more low anterior resections are being performed for lesions in this area. It appears to make no difference whether a stapling device is used to perform the anastomosis or not. The issue is not what method is used to do the anastomosis, but whether or not clearance can be obtained distal to the lower level of the tumor. Although it was originally thought that a minimum of 5 cm was needed distal to the lower level of the lesion, modern thinking is that for almost all patients, 2½ cm is probably sufficient. With good anesthesia, relaxation and good mobilization of the rectum it is possible to perform a suture line within 2 to 3 cm of the anal verge. A temporary colostomy may or may not be used to complement the anastomosis.

Another change which has taken place has been in the management of the small cancer of the distalmost rectum. In former years all these tumors were managed by abdominoperineal resection. Today, however, small tumors (3 cm or less) superficial in nature and well differentiated are managed without abdominoperineal resection. The methods that may be employed include full thickness excision by the transanal route, or for anterior lesions approaching the rectum through a posterior midline incision splitting the sphincters, opening the rectum, excising the tumor, and then closing the rectum.

Another technique which has been popularized by Sichey in upstate New York and Papillon in France is the concept of treating these small lesions with endocavitary radiation. Eleven thousand to twelve thousand rads are delivered by low voltage within the anus over a period of a number of weeks. Sichey has reported 95% local control with this method. Again, the most important point in the choice of patients is the differentiation of the tumor. The tumor must be well differentiated, small, and mobile.

Adjuvant Therapy. Dr. Shafir describes our GI-Tumor-Study-Group trials using adjuvant therapy. One trial involved adjuvant chemotherapy or immunotherapy or a combination given to patients with potentially curable colon lesions of the intraabdominal colon. The results were similar in all groups: control, immunotherapy, chemotherapy, or combination immunochemotherapy. We concluded from this that adjuvant chemotherapy plays no role whatsoever in the management of abdominal colonic cancer. I will make that as a flat statement.

Radiotherapy plus Chemotherapy. On the other hand, in a trial of combination radiotherapy and chemotherapy in rectal cancer, one group received radiotherapy (about 4,400 rads), plus 5-FU starting 6 weeks postoperatively followed by 5-FU and methyl-CCNU for 18 months. Two other groups received either chemotherapy alone or radiotherapy alone. The results of the combination were statistically superior to the results for the controls. Early on in the study we eliminated the control because of ethical considerations. We broke the code because one group was doing badly, and that group turned out to be the control. There is, however, no statistical difference in disease-free survival between the three treatment groups. When we look at the overall survival there again appears to be an advantage to the combination group, but this is not statistically significant.

So it appears that adjuvant therapy, giving radiotherapy and chemotherapy, delays the appearance of recurrence, but apparently does not influence overall survival. If this effect is at low cost, it may very well be worthwhile. On the other hand, one must remember that in the GI Tumor Study Group in that early colon study, 6 patients developed acute leukemia, possibly secondary to methyl-CCNU, because all of those patients with leukemias were in the group that received methyl-CCNU. I think there are now other reports of these agents producing leukemia.

Radiotherapy. One Veterans Administration study appears to show that preoperative radiotherapy is of advantage in rectal cancer. It appears from the data, since all comers were randomized, that the number of patients found on pathologic examination after surgery to have positive lymph nodes was much lower in the radiated group. So radiotherapy given preoperatively clearly has the ability to shrink the tumor and make a large bulky inoperable tumor resectable, and radiotherapy probably does influence lymph nodes. Postoperative radiotherapy appears to have some advantage; several trials are under way giving a small preoperative dose, then surgery, followed again by therapeutic amount of postoperative radiotherapy. There are no good data on that at the moment.

Surveillance

Finally, it seems to me that if we are really going to attack this disease, we are going to have to be able to know how to find it at an early stage. I think every patient over the age of 40 years should have their stools examined for blood every time they go to a physician's office. Cancer of the colorectum is a public health hazard, and certainly people known to be at risk must be kept under constant surveillance. Surveillance for patients of polyp families includes periodic sigmoidoscopy, colonoscopy, or barium enema starting at an early age. One can say the same thing about surveillance involving the nonpolyp syndrome, starting at a later date. With ulcerative colitis we now begin surveillance programs of colonoscopy and biopsies looking for dysplasia at about the eighth year of disease.

Certainly the most important group to be kept under surveillance is the patient who has had an adenoma diagnosed in the past; also, anyone with a history of cancer anywhere in the family, any woman who has had breast cancer, and any patient with inflammatory bowel disease. Using this kind of an approach we are going to do more as a group to cut the death rate from colorectal cancer than by worrying whether we should cut it out, burn it out, scrape it out, x-ray it, or give injections to get rid of it.

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Treatment of Hepatic Metastases

Roy B. Jones, M.D.

To begin, I shall depart somewhat from the topic of how to deal with hepatic metastases and discuss in a broader framework the route of administration and the pharmacology of antineoplastic agents. I'm a pharmacologist by avocation. The surgical anatomy of the liver and abdomen is particularly important in addressing the subject that Dr. Aufses reviews, that is, how to deal with colon carcinoma, colon carcinoma that perhaps has already spread in an occult fashion at the time of initial diagnosis.

First, I shall review a few pharmacologic concepts in order to emphasize the interaction of the pharmacology of antineoplastic agents with anatomy. This approach should allow us to design concepts about how to use chemotherapy more effectively.

The current standard buzz term in the pharmacology of neoplastic diseases is "C × T area"—the area under the curve plotting drug against time. The concentration of the drug in the plasma is plotted on the vertical axis; time is plotted on the horizontal axis. The C × T area in effect is an integral under this curve and represents the exposure of a tissue to the drug over the period of time the drug has been given (Fig. 1).

Clearance. We are all familiar with creatinine clearance as a measure of the excretion of creatinine into the urine and indirectly as a measure of renal function. Similarly, drug clearance can be measured by dividing the dose given by the C × T. This yields a clearance measurement expressed in ml/min, like the creatinine clearance. Just as creatinine clearance measures the disappearance of creatinine into the urine, clearance of a drug, for example 5-fluorouracil, from the plasma can be described by this kind of calculation.

Extraction. In using regional chemotherapy, we must know how much of the drug disappears into the tissue of interest and how much gets through and circulates throughout the body. In medical oncology, the big problem is that the drug interacts with normal body tissues adversely, causing major toxicities and limiting the treatment we can give. *Extraction* can be defined as the amount of drug that goes into the tissue minus the amount coming out divided by the total dose administered. This measure tells us how much of the drug is really deposited in the tissue that we want to treat.

Variables in Regional Chemotherapy

Three types of major variables affect the effectiveness of regional chemotherapy: physiologic, pharmacologic, and clinical.

Physiologic Variables. Two major physiologic variables affect regional chemotherapy. First, tumor blood flow as a percentage of total cardiac output—this should be very low. To illustrate, a tumor may have a total blood flow of 100 cc/min in a patient with a cardiac ouput of 6 liters/min. An intravenous injection that goes to the entire body may deliver only 2% of the dose to the tumor and 98% to normal tissues. Direct infusion of the tumor might be capable of reversing this ratio.

The second important physiologic factor is whether or not the blood flow to the tumor can be effectively isolated. If six blood vessels supply the tumor, only one of which is catheterized, most of the tumor is perfused by blood with a low drug concentration.

With respect to blood flow and the liver, the average person has a total liver blood flow of about 1,600 cc/min. Two-thirds of that is usually portal blood flow and $^1/_3$ is hepatic artery blood flow. The total cardiac output is 5 to 6 liters/min. Note that many areas of the body have relatively low blood flows and these are optimal for regional

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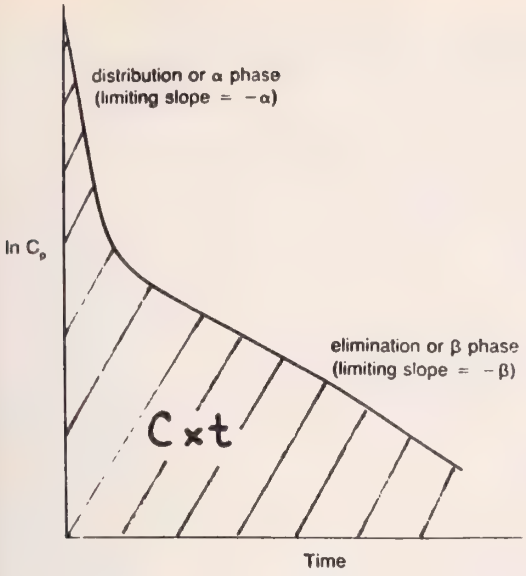

Fig. 1. Two-phase behavior following bolus input of two-compartment model.

chemotherapy from the point of view of the circulation.

Pharmacologic Variables. What pharmacologic variables affect the utility of regional chemotherapy?

First, using the concept of extraction, obviously we would like to have the tissue of interest extract a high percentage of the drug. If 100 gm of 5-fluorouracil (5-FU) are given into the liver and 95 grams are absorbed in the liver or the liver tumor and only 5 get out, that's going to minimize toxicity in other places in the body, a desirable circumstance.

Second the total body clearance of the drug should be high. That is, once that 5 gm goes into the systemic circulation, it should, ideally, be metabolized or eliminated very rapidly. Thus, other tissues will not be affected by the drug and the toxicity will be minimized.

Finally, a point of paramount importance that is sometimes ignored in studies of regional chemotherapy, the parent drug or a metabolite which can form in the tumor bed must be active against the tumor. For example, there are a number of drugs that must be metabolized to become active. If the perfused tissue cannot metabolize the drug, the regional advantage is lost. Cyclophosphamide must be metabolized by the liver to become active. If this drug is given into a sarcoma in a muscle, the treatment would be of little use, because the substance is the pro-drug and not the active drug itself. So a knowledge of what chemical species mediate drug activity is important.

Metabolism of Active Drugs. The fluorinated pyrimidines, fluorouracil and FUDR are drugs as active as any compounds in the treatment of colorectal cancer. They are of high interest in relation to regional chemotherapy in the liver.

In addition to knowing just which drugs are active against the tumor and how these drugs are metabolized, we must know the capacity of the body organs for metabolism. For example, consider the disappearance of 5-FU when it is given regionally into an organ that is capable of metabolizing it. In perfusing with increasing doses, there may come a point at which the plasma levels of drug drop less rapidly. This happens because there exists a catabolic pathway for the drug in the liver and, like any kind of metabolic pathway, it can be saturated. If more drug is given than the pathway is capable of handling per unit of time, rapid increases in drug delivery to plasma are noted. It is important to think about different rates at which a drug might be delivered. One can give a very rapid bolus of drug, causing plasma levels to go very high and then rapidly come down; one can give a slow infusion and the drug levels will be low at any point in time. If there is a saturable metabolic pathway involved, and one gives the drug in a large bolus dose directly into the hepatic artery, the catabolic pathway of the drug may quickly become saturated. Most of the drug may escape from the liver, resulting in little therapeutic effect and high toxicity. On the other hand, a low-dose, continuous infusion of the drug into the liver may well not saturate the metabolic pathways. Thus, the levels of drug presented to extrahepatic tissues would be quite low and the total amount of drug presented to the tumor would be quite high.

Clinical Variables. Obviously, we want to use drugs whose toxicity in perfused normal tissue is low. For example, if a hepatic-artery infusion is done, we'd use a drug that doesn't cause hepatic inflammation and hepatic toxicity. The likelihood of significant distant tumor metastasis also should be low. This is a frequent clinical problem. In a patient who has metasatic colon carcinoma in the liver and other sites, treating the tumor in the liver regionally and ignoring the rest of the disease will probably be of minimal overall benefit to the patient.

Also, the probability of morbidity without treatment of the perfused tumor should be high. That is, the risk of surgically implanting a catheter into the liver and subsequent treatment must be justified on the basis that if some intervention is not made against that particular tumor

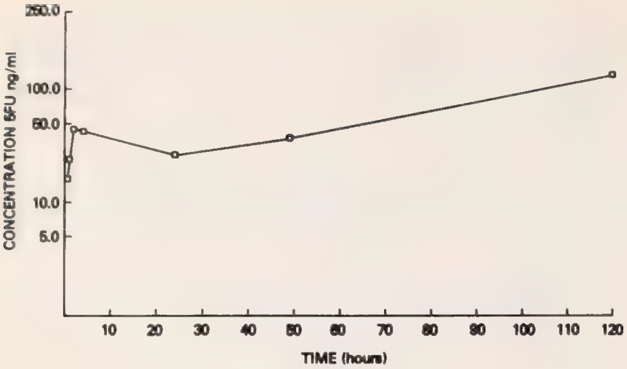

Fig. 2. Plasma concentrations of fluorouracil in patient receiving continuous infusion (30 mg/kg/24 hr) via hepatic artery.

in the liver, the patient will suffer substantial adverse consequences.

Again, I want to make a point about 5-fluorouracil. We have data demonstrating that when given intravenously at low doses, fluorouracil disappears from the plasma vary rapidly. At higher doses, the disappearance can be slowed because fluorouracil catabolic pathways have been saturated.

In a patient being treated with fluorouracil, if the liver function is normal, the levels of fluorouracil in the blood are described typically by a very high peak and a very rapid falloff curve. But in a patient who has extensive hepatic metastasis, there will be a prolonged fluorouracil half-life. As a patient develops increasing numbers of hepatic metastases or other diseases that affect liver performance, the capacity of the liver to metabolize fluorouracil may diminish to the point that there are prolonged high levels of fluorouracil in the blood, greatly magnifying the risk of extrahepatic toxicity.

With a continuous infusion of fluorouracil via the hepatic artery, the following pattern typically emerges: Very rapidly levels in the blood achieve what seems to be a plateau; but later, up to 120 hours later, there is a rise in the level of drug in the plasma (Fig. 2). Over time, the metabolic pathways become saturated, even at a low dose-rate, and eventually toxicity is going to supervene.

Numerous recent articles have described the use of intermittent low-dose continuous drug infusion, given by a totally implantable pump in the treatment of hepatic metastases. A 75% to 80% response rate of liver metastasis from colon cancer has been reported. This kind of response rate is not unique, in fact, a high level of response was reported by Ansfield and others as much as ten years ago (Table 1). Unfortunately, in many patients with a high response rate, there may be disease outside the liver. Also, the surgical placement of a catheter may involve risk and toxicity.

In one study of 419 cases in which hepatic arterial-infusion catheters were placed, catheter displacement was found to be relatively common (Table 2). Catheter cracking or leaking happens often. Infection of the percutaneous catheter entry occurs perhaps a little less so. Several other complications are possible. Anytime these catheters are put in, risk of toxicity from the surgical procedure in catheter placement has to be considered.

There are several ways by which catheters can be placed, but one difficult problem is to reduce the arterial circulation to the liver tumor. If the hepatic artery is ligated, the liver and tumor can obtain blood from diaphragmatic arteries and other sources. This often happens within a period of just a few days after hepatic artery ligation. One of the problems of treating hepatic metastases is that the isolatability of the blood supply of the liver is not high. This greatly limits the kinds of techniques that may prove effective when one tries to give perfusional treatment into the liver.

In the implantation of a subcutaneous pump, a silastic catheter is placed onto a tributary of the hepatic artery, without ligation of the hepatic artery itself. The tube is passed into the hepatic artery and then into either the common hepatic artery or a branch of the hepatic artery which supplies the tumor. Often angiographic dyes are injected at high speed to see if the particular circulation of the tissue to be treated is being perfused. The blood flow of the hepatic artery is about 8 cc to 10 cc per second, and the typical gun used to inject radioiodinated contrast material into the liver has an injection speed of between 3 cc and 7 cc per second. At that rate, there is a major distortion of the hepatic blood flow and radiographs may give a false picture of physiologic perfusion patterns. Several investigators have now developed the technique of slow-flow angiographic evaluation, using radiolabeled microaggregated albumin, given at a flow rate of 0.8 cc to 1.0 cc per second. By taking serial pictures using a gamma counter, one can see that the entire liver tumor is perfused. In the same patient, a high-speed injection might make it appear as if one portion of the liver was being perfused.

The totally implantable Infusaid pump contains a freon-type material in a bellows that sur-

TABLE 1
Fluoropyrimidine Liver Perfusion

Reference	Schedule (mg/kg/d)	No. Pts.	Prior 5-FU	Response (>50% ↓)
5-Fluorouracil				
Ansfield Cancer 36:2413	20–30 × 4d 15 × 17d	419	75%	55% of evaluable 38% of total
Fortuny CTR 59:401	25 × 7d	12	? none	83%
Rochlin SG&O Sept. 1976	10 × 14d	24	N.S.	50%
Burrows	20 × 10d	39	N.S.	73%
Cancer 20:1886	40 × 5d	29	N.S.	58%
Massey	15–30 × 21d	28 G.I.	N.S.	43%
A.J.Surg.121:160		5 breast	N.S.	40%
	(3 responses in 6 patients resistant to i.v. 5-FU)			
5-FUdR				
Watkins SG&O Apr. 1970	20 × 21–42d	82	N.S.	71% (criteria unclear)

rounds the chamber where the drug is contained. There is a small injection port where the drug can be injected into the pumping chamber. As you inject it, the freon-type material turns from a gas to a liquid as it is compressed. Body heat, in a slow but controlled fashion, will reconvert this matter from a liquid to gas, putting pressure on the chamber and thus causing infusion of the drug at a slow rate. These chambers can be calibrated at the factory to produce a given flow rate, depending on the requirements of the individual patient.

This technique still has major limitations. Even though for patients with hepatic colon cancer metastasis there is up to a 75% to 80% partial response rate of the liver metastasis, there has as yet been no demonstration in randomized controlled trials that this regional therapy prolongs survival. Also, in patients with liver metastasis from colon cancer, almost 75% have an intraabdominal or extrahepatic cause of death after recurrence. The perfusion of the liver metastasis allows palliation of patients who have primary liver metastases of clinical importance, but in the long run probably will not have a major impact on almost 75% of patients with colon cancer who have recurrent disease. This may be one of the explanations for the failure to achieve prolonged survival in most patients when such adjuvant treatments are tried, particularly treatments which primarily address the liver metastases.

Directions for Exploration

I shall end by briefly considering the relationships between the anatomy of the disease, the anatomy of the patient and what we understand to be the pharmacologic principles involved in fluorinated pyrimidines. This suggests new ways which might be explored in treating patients with colon cancer who are at risk of or have actual widespread metastases.

In using 5-fluorouracil, we see, typically, a peak plasma concentration in the range of 0.3 millimolar to 1 millimolar. Because of the kinetics of fluorouracil, that concentration is only maintained for about five to ten minutes. This dose results in leukopenia and possibly mucositis

TABLE 2
Morbidity Resulting from Intrahepatic Artery Infusion, 419 Cases

Morbidity	No. of Pts	%
Catheter displacement	45	11
Catheter cracking or leaking	21	5
Infection at site of percutaneous catheter entry	16	4
Upper GI bleeding	11	3
Infected mycotic aneurysms or peripheral septic embolization	5	1
Clotted catheter	5	1
Hepatic artery occlusion	5	1
Nonfatal stroke	1	—

for a significant percentage of patients who receive it. Colon cancer cells in culture require a dose in the order of 1 millimolar before a substantial fraction of colon cancer cells are destroyed. So one of the ways we can look at the problem from a pharmacologic point of view is, how can we generate this kind of drug concentration for hours or days (instead of for three or four minutes) in an attempt to kill residual colon cancer cells in these patients?

Consider now plasma levels from a clinically achievable dose given by hepatic-artery infusion of fluorouracil. Instead of the 1 millimolar plasma concentration one sees with the intravenous injection, there is a micromolar or submicromolar concentration in the plasma. This occurs because the liver is capable of metabolizing the fluorouracil and limits the exposure of normal tissues outside the liver to fluorouracil, so one can give a very high dose directly to the liver without achieving such high plasma concentrations.

We are beginning to explore related but different concept. Can we use liver metabolism of fluorouracil in addressing not only the risk of hepatic recurrences of tumor but also the risk of local-regional recurrences of the colon cancer? A technique which might be helpful is intraperitoneal chemotherapy. (Dr. Shafir has alluded to this in his paper on cancer therapy.) The technique involves giving the drug in a large volume of fluid into the peritoneal cavity. As experimenters have known for 30 years, when you inject a drug into the peritoneal cavity of a rat, it exits from the peritoneal cavity through the portal circulation, the major venous drainage bed of the mesentery and the peritoneal cavity. The same principle applies in humans. We can thus exploit the liver's capacity to metabolize fluorouracil by giving the drug intraperitoneally.

We use an implantable Tenckhoff catheter for this purpose (Fig. 3). We give the drug in a large volume of fluid so that the maximal extent of peritoneal surface will be exposed to the drug. And we hope to treat the liver also as the drug drains into the portal circulation while exiting from the peritoneal cavity. Note that studies of both humans and rats have shown that micrometastases spread hematogenously from local colon cancer to the liver. Only when metastatic tumor becomes larger than 30 mg and is almost clinically detectable is there significant arterial blood supply.

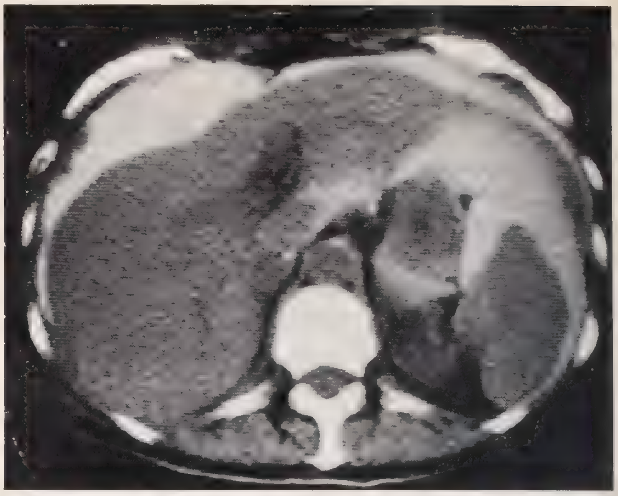

Fig. 3. CT scan of abdomen; interperitoneal "white areas" represent contrast-containing dialysate, administered through Tenckhoff catheter demonstrating good spread of drug throughout peritoneal cavity using this high-volume technique.

So, it is conceivable that intraperitoneal fluorouracil would be the ideal way to deliver drug to a patient with Dukes' C colon cancer with occult liver metastases. Perhaps the use of this technique in such an adjuvant setting would be the optimal pharmacologic and anatomic way to deliver 5-flourouracil. We have shown that using this technique one can give millimolar concentrations of fluorouracil in the abdomen and to the liver for 48 consecutive hours with no systemic toxicity.

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Breast Cancer: Which Operation?

Angelos E. Papatestas, M.D.

What operation should we do today for breast cancer? I cannot give a simple direct answer. What I'll try to do first is to discuss why we have come to the point of raising the question.

For about half a century, the surgical treatment of breast cancer essentially was limited to one procedure only: radical mastectomy. The situation is different today and raises many issues.

Physicians approach the question of treatment of breast cancer and of any other disease after evaluating empirical observations and scientific knowledge. The patients who come for treatment of breast cancer, today at least, approach the question in a slightly different way. The threat of losing a breast has a devastating emotional impact, and the dilemma that women formerly had to face—either lose your breast or jeopardize your life—clearly does not exist and its presentation to patients has been eliminated by law, at least in California and Massachusetts. Given an option on such a critical issue, women will challenge the dogmatic physician. In this era of the educated consumer, we hear about women shopping for surgery. The surgical "supermarket" today offers a wide selection of treatments, all considered acceptable:

- Mastectomy
  - extended radical
  - radical
  - modified radical
  - simple with axillary dissection
  - simple
- Breast-conserving operations (with or without axillary dissection or sampling)
  - partial mastectomy
  - quarantectomy
  - lumpectomy

It is obvious that if all these procedures are being practiced today, there must be advantages and disadvantages in each, and proponents for each approach. Therefore I raise three additional questions that may help us think through the choices:

- What is the role of surgery in this disease?
- What is the definition of *operable breast cancer?*
- What is the nature of the disease?

If we focus on the third question, we will understand what has changed our approach to the surgical treatment of the disease.

The Nature of Breast Cancer. Breast cancer should be considered a systemic disease by the time it becomes clinically manifested as a localized tumor. Dr. Holland discusses the concept of polycytoma and that 1 billion cells make a palpable lesion. The clinically obvious tumor already has 1 billion cells, and it is realistic to suspect that some of these malignant cells are already outside the main lesion and that therefore the disease should be considered systemic. This does not necessarily imply that there will be clinical manifestations of systemic disease, either at the time of the appearance of the primary tumor or in the subsequent follow-up. What we can predict, though, is that in over 50% of women with a malignant breast tumor, with histologically confirmed node involvement but with no clinical manifestations of systemic disease, there will be subsequent clinical metastases, and therefore these patients cannot be treated effectively with local approaches only, that is, with surgery alone.

The operation selected should not only allow histologic confirmation of malignancy in the breast tumor, and be effective for local control, but should also determine the degree of axillary node involvement in order to define those patients who in addition to surgery require systemic treatment for the control of disease. Clinical evaluation of axillary node involvement is inade-

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quate, since the margin of error between clinical staging and histologic evaluation is in the order of 25% in either direction. Therefore, relying on clinical findings only, we can incorrectly stage a patient as having no involvement of the axillary nodes and not advise systemic therapy, when in reality the patient would benefit from it.

In addition to this diagnostic exploration of the axilla, the role of the surgeon is to handle properly the surgical specimen in order to determine other different parameters—the hormone sensitivity of the tumor, the grade of malignancy, and the like—that appear to have a prognostic significance and that could have major importance in selection of appropriate treatment. I'll come back to that point later.

Operable Breast Cancer. Now, what is the answer to the second question, and what does the term *operable breast cancer* mean? With the current understanding of the role of surgery, almost all tumors should be considered operable. But the aim of the operation differs in relation to the stage of disease. If a tumor is of limited extent—T1 NO or T2 NO (Union Internationale Contre Le Cancer, UICC standardized staging for breast cancer)—then the operation can be curative. But even with tumors that are larger, that is, T3 tumors and those which in previous years were considered inoperable, surgical palliation in combination with chemotherapy and radiotherapy has a major role because of the advantage that debulking gives to the systemic treatment of the disease.

The Role of Surgery

These concepts lead us to the answer to the first question. The role of surgery is not only to treat the disease; surgery is also a diagnostic and exploratory method that aims to determine what is the best local treatment, whether the patient should receive systemic treatment, and what type of systemic treatment this should be. The surgeon should also decide whether the aim, at least from the point of view of local control, should be to cure or to palliate. So we are observing a major revision in our understanding of the role of surgery in the treatment of breast cancer. Surgery, previously defined as protective against the spread of disease, is now viewed as aiming at local control and as enhancing the effectiveness of the adjuvant treatment. The role of node dissection, previously considered to be curative, is also viewed differently now, since we accept that when a patient has many nodes involved, regardless of the extent of surgery, the patient will not be cured by surgery. It is important to know if the patient has nodes and how many nodes are involved in order to determine the best treatment for the patient, but the role of node dissection is mainly exploratory, aiming ~~to properly stage and also to debulk~~ the tumor.

Systemic Disease and Local Tumors. The concept that there is systemic disease even with localized tumors has led to the controversy about the choice of surgery. This controversy was accentuated by the publication of many well-documented studies which indicated that lesser treatments than radical mastectomy appear to have as good results as radical mastectomy. We have now reached the point of accepting what a few years ago was heresy—that radical surgery is not the only solution. This is now confirmed by the randomized studies and Fisher's National Surgical Adjuvant Breast Protocol (NSABP) that compared (a) in patients with clinically negative nodes, the results of radical mastectomy versus simple mastectomy with radiation, versus simple mastectomy without radiation; (b) in patients with clinically positive nodes, the results of radical mastectomy versus simple mastectomy with radiotherapy. The results are more or less well known and the study continues its follow-up beyond the five-year period. Up to now, at least, there has been no significant difference in the overall survival of patients, but there has been a difference in the rate of local failure, which indicates that the choice of the surgical treatment does not significantly affect survival. Even though the local reappearance of the tumors will necessitate further local treatment, it apparently does not significantly influence the outcome of systemic disease.

It was obvious that after this door was opened, a second study would be necessary to evaluate even less radical approaches and breast-conserving operations. Such a study is the NSABP no. 6, which essentially compares mastectomy with breast-conserving operations, with or without irradiation. All patients have axillary dissection for staging purposes, and those with positive nodes receive adjuvant chemotherapy. The results of this study have not been published as yet, but Dr. Fisher has reported that the results are similar to those of studies in Milan and at Guy's Hospital in London which show that breast-conserving operations result in essentially the same survival figures as those observed following mastectomy; again, however, there is a difference in local recurrence figures. So we are awaiting the results of the Fisher study and a

National Cancer Institute study to determine whether they will confirm that the choice of local treatment does not influence appearance of distant disease. If this is confirmed, we can safely predict that in the future, our primary aim in selecting a surgical treatment will not be to improve the overall survival figures but to decrease the rate of local reappearance of tumors. It seems that factors unrelated to the type and extent of surgery many influence the rate of local failure.

Local Failure. The rate of local failure following mastectomy or breast-conserving operations varies in relation to the presence and the number of nodes that are involved. Patients with large tumors and with extensive axillary-node involvement will have a much higher rate of local recurrence than patients with small tumors and no involvement. It appears, therefore, that the number of affected nodes is an important determinant affecting not only survival but also local recurrence. This finding confirms previous studies which showed that tumor stage and tumor size are important factors affecting curability, regardless of treatment. Aggressiveness of the tumor is another important prognostic determinant. Consider prognosis within a stage of breast cancer—the T1 NO MO stage—that appears to be more or less curable with a variety of surgical methods ranging from radical to conservative; the effect of factors that are unrelated to the treatment but that essentially reflect the aggressiveness of the tumor is to create marked differences in ten-year survival. Tumors with two or more aggressive characteristics are associated with ten-year survival of 50%, versus almost 100% survival at ten years for tumors which do not have aggressive characteristics.

It looks as if we have been barking up the wrong tree for a long time, concentrating on indiscriminate, aggressive surgical treatment, rather than defining the nature of the disease and characterizing specific subgroups in relation to aggressiveness of the tumor, and modifying our treatment accordingly. Even today, most of the studies that evaluate alternate surgical methods of treatment, with breast-conserving surgery, involve patients with early tumors, so we cannot extrapolate about the effectiveness of such treatments in patients with larger and more aggressive tumors.

What is the theoretical disadvantage of breast-conserving operations? It is very clear what the potential problems are (Table 1). Any procedure that conserves breast tissue may be leaving the patient at risk for local reappearance of the disease; studies of mastectomy specimens reveal multifocal disease in 13%–74% of the patients.

TABLE 1

Incidence of Multifocal Disease (Invasive and Noninvasive)

Fisher et al	1975	13%
Lagios et al	1981	28%
Lesser et al	1982	30%
Patchefsky et al	1977	47%
Qualheim et al	1957	54%
Gallager et al	1970	79%

What influences multifocal disease? Unfortunately, we don't know. If we knew, then we would be able to say that in those patients without characteristics of multifocality, breast-conserving operations could safely be performed. We don't even know whether in situ lesions evolve necessarily into clinically palpable or invasive tumors. Reviewing the literature for the percentages of local recurrence of local failures in relation to a specific procedure, one does not find reliable or consistent numbers, even after stratifying for stage of disease, because the reports cover wide and overlapping ranges of local failures for each procedure within each presenting stage of the disease. Essentially, the available evidence doesn't allow us to characterize the group of patients for whom lesser procedures than mastectomy could be done without increasing the risk of local failure because of the presence of multifocal disease.

Survival Rates. The reason I have said that we may be barking up the wrong tree is made very clear by Table 2. Prognosis is affected by factors unrelated to treatment; that is, it is affected not only by treatment but also by tumor characteristics and host resistance. If you examine the results of mastectomy in relation to the aggressiveness of the tumor and the host resistance, you see markedly different five-year survival rates. For those patients who have highly differentiated tumors and marked reactivity in the regional

TABLE 2

Five-Year Disease-Free Survival in Relation to Tumor Differentiation and Hormone Receptors (Number = 341)

Estrogen or progesterone levels	Tumor differentiation	
	Well & Moderate	Poor
Positive (≥10fm/mg cytosol protein)	64%	53%
Negative (<10fm/mg cytosol protein)	54%	40%

Patients treated at The Mount Sinai Medical Center.

lymph nodes as measured by the presence of histiocytes—that is, a favorable combination of highly differentiated tumors and marked reactivity—five-year survival surpasses 90%, which is exceptionally high. But for patients who have the unfavorable combination of poorly differentiated tumors and minimal reactivity in the regional lymph nodes, five-year survival is approximately 40%. We see more pronounced differences than those observed when comparing different treatments, which means that the material we are comparing when we try to evaluate different treatments without taking other factors into consideration is not very homogeneous.

Summary

What we can say today is that when treating the primary tumor, the extent of surgery beyond the "cancer operation" for that tumor (that is, removal of the lesion with a margin of healthy tissue around it) will not directly and significantly influence survival but will influence the risk of local reappearance of the tumor in the same target organ, which may eventually affect the course of the disease.

Therefore, coming back to the key question of the discussion today—What operation should be selected?—the indirect answer is that since the extent of surgery after the complete excision of the tumor does not influence survival, the selection of operation should be based on the presence of factors that predict the probability of local recurrence. More studies of these factors are needed. In the meantime, with available knowledge, I think that if we want to minimize the risk of reappearance of the tumor of the breast the safest operation is still a simple mastectomy with axillary dissection for early lesions. Breast-conserving operations should be limited to women with early lesions who have tumors that do not display aggressive characteristics. Since our topic was choice of operation and not combination of modalities, I will not discuss adjuvant or alternate local treatment (radiation) or palliative surgery for advanced breast tumors.

Discussion

Question: How do you treat a local recurrence?
Answer: If the initial workup is negative for any evidence of metastatic disease, then a local recurrence treated with wide surgical excision and adjuvant chemotherapy may give surprising results in terms of length of survival. I don't think that recurrence is necessarily a manifestation of systemic disease. It may be a delayed clinical appearance of tumor foci that were left behind during the initial surgery of the primary tumor.

Question: Could you comment on the treatment of intraductal carcinoma of the breast, noninvasive?
Answer: I think the same principle should be applied as for invasive cancer, because there is no accumulated evidence clearly defining the subgroup of women in whom the potential risk for development of a malignant invasive tumor is high. In contrast to the risk that exists in lobular in-situ carcinomas, where invasiveness is expressed in long term follow-up, and there is an increasing risk with increasing time, expressed bilaterally, the risk in intraductal carcinoma is mostly expressed unilaterally within the first few years after the initial appearance. So, I would advise, have a mastectomy, if the maximum risk protection against local failure is the aim. In patients who are aware of risk of the local failure and who elect to have breast-preserving approaches, I would be very careful in the initial follow-up period, during which time most of the risk is expressed. The aim would be to detect early any subsequent appearance of an invasive lesion. But my advice would be to have a mastectomy, although I think a lot of patients at this point would elect not to follow it, and their choice, if they are well informed on the risk of local failure, should be respected.

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Thoughts on the Surgical Staging of Lymphomas

LARRY NORTON, M.D.

While the role of surgeons in the staging of the malignant lymphomas is still vital, it is clearly changing. The essential step in the diagnosis of a lymphoma is a surgical biopsy, thoughtfully obtained and carefully processed. However, the staging laparotomy, once the principal source of prognostic information, the premier step in treatment planning, is now important in fewer cases. This shift in standard practice is due to an expanded role for chemotherapy, improved understanding of the natural history of disease, and better methods of noninvasive diagnosis.

Cancers of the lymphatic tissue are commonly categorized as either Hodgkin's disease or non-Hodgkin's lymphoma. This either-or terminology is unfortunate because it confuses many distinct diseases. Let us consider each of these two broad classes of cancer separately, using our advanced knowledge of the surgical staging of Hodgkin's disease to illustrate issues of general importance.

Hodgkin's Disease

As pointed out by Vincent DeVita, Jr., the surgical staging of Hodgkin's disease was of major historical value and taught many lessons on natural evolution and clinical behavior that could not have been learned by other means. We learned that Hodgkin's disease was orderly, progressing from the area of the lymph node to adjacent areas, then to contiguous organs, and eventually to distant nonlymphatic sites. We learned that the diaphragm was an important anatomical divider, and that once Hodgkin's disease spread from above to below the diaphragm, the clinical behavior of the tumor was different. We learned that for patients without organ involvement, involvement of the high paraaortic nodes only carried a different therapeutic implication from involvement of the lower chain. We learned to correlate nonsurgical tests like lymphangiography with anatomical realities, and to interpret data from noninvasive testing so as to be clinically meaningful. We even learned the utility and limitations of the kinds of surgical procedures—percutaneous liver biopsies and bone marrow biopsies—that internists could safely perform.

Indications for Staging Laparotomy. However, in the management of an individual patient, we must reexamine the importance of the staging laparotomy. It is a good rule in all of medicine that we should only perform a test if the results of that test will influence our clinical judgment. Hence, the staging laparotomy should be done only when it will be used to plan therapy. If by nonsurgical techniques we have learned that a patient needs chemotherapy, for example, and that radiation alone would not suffice, an exploratory operation is contraindicated. Clearly, radiotherapy is important for localized, anatomically limited disease. Disseminated disease, however, must be treated by drugs, sometimes in conjunction with radiation, often alone. If we have evidence of dissemination, therefore, further surgical evidence of dissemination is superfluous. The decision on whether to operate must be made in the total therapeutic context.

The therapeutic environment may vary between institutions. In general, however, very early stage Hodgkin's disease is treated with radiotherapy alone. This usually includes patients with Stage I disease, involving a single lymph-node area, or Stage II disease, involving two adjacent areas on the same side of the diaphragm. A patient with cervical lymphadenopathy, for example, proven by biopsy to be Hodgkin's disease,

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must be examined systematically for more advanced disease that would indicate the need for more than radiotherapy alone. A history and physical examination, with particular attention to adenopathy, hepatomegaly, and splenomegaly, are essential. "B" symptoms of weight loss, episodic sweats, fever, and generalized malaise, or serum chemical or hematological abnormalities, may indicate the need for special scrutiny. A negative chest x-ray must be followed by tomography or computerized axial tomography. Bilateral bone-marrow biopsies should be performed if a unilateral sample is negative. While a bone scan positive in multiple sites is usually evidence of disease involvement, positive results in one site only must be followed by biopsy. Abdominal examination should involve lymphangiography (LAG), if the CAT is normal, and liver scan and percutaneous or even laparoscopic liver biopsy if the LAG is normal. If, after all of these procedures, there is no evidence of disease outside of the Stage I or II distribution, we are left with what is essentially a therapeutic decision. If a true Stage I or II patient is to be treated with radiotherapy alone, it may be necessary to perform an exploratory laparotomy to prove the absence of intraabdominal disease. Yet, for patients with bulky Stage II disease or for those with "B" symptoms, the treatment may be both radiation and chemotherapy. It therefore would not be necessary to search for microscopic abdominal disease, as the patient will get chemotherapy anyway, and no bulk sites of abdominal disease (which would require radiation) were seen on CAT and LAG. Also, some institutions find that patients who receive radiotherapy for Stage I or II disease, and who attain complete remission but later relapse, have an excellent chance of going into complete remission again if chemotherapy is applied. Therefore, even in the special case of early-stage Hodgkin's disease, exploratory laparotomy may be indicated only rarely.

Progress of Hodgkin's Disease. Because of the involvement of the surgeon in these important decisions, specific knowledge of Hodgkin's disease is of value. While the orderly progression from node to node is the rule, there are exceptions. For example, some—as many as 15%—of patients with massive abdominal disease and clinically positive left cervical lymph nodes may have mediastinal nodes free of disease. This suggestion of lymphohematological spread is the only common skip lesion in Hodgkin's disease. Involvement of Waldeyer's ring in the oropharynx or epitrochlear nodes is so uncommon in the disease as to raise serious questions about the diagnosis. We have recently learned that direct extension of Hodgkin's disease from nodes into surrounding tissue—the Ann Arbor "E" classification—does not necessarily mean that the disease belongs in the higher category of Stage IV, for these patients often demonstrate a response to radiotherapy and recovery associated with nodal involvement only.

The radiotherapy of patients with Stage $IIIA_1$ Hodgkin's disease is quite successful. These are patients without symptoms who are found to have nodal disease above the diaphragm and only in the upper portions of the paraaortic chain. Patients with IIIA disease who have lower lymph node involvement, however, may need chemotherapy to maximize their chances for cure, so surgical exploration may be of value. That is, if after an exhaustive search as outlined above, a patient seems to have only $IIIA_1$ disease, biopsy of the lower paraaortic nodes may be needed. The wide use of CAT has confused rather than clarified this situation; rarely does this most modern of tests fail to reveal at least a single one-by-one-centimeter lymph node in this area. We may find, as our experience grows, that patients are being subjected to surgery unnecessarily in some of these cases, a possibility that demands our most careful attention.

Patients with Stage III nodal disease with "B" symptoms, or those with true Stage IV disease with extranodal involvement, are affected, of course, by the most advanced forms of Hodgkin's disease. A few short decades ago, these patients were uniformly doomed to die of their disease. The introduction of polychemotherapy for Hodgkin's disease, particularly the MOPP regimen, was one of the major advances for oncology in the modern era. At present, about two thirds of all such advanced cases can be expected to enter complete remission on chemotherapy, and two thirds of these will be cured. Many new ideas for using chemotherapy with radiation, and several different chemotherapy regimens together, may improve these odds even further in the future.

Surgical Management. Using all of this knowledge of the stages and complexities of Hodgkin's disease, how are we to surgically manage the patient with isolated lymphadenopathy? About 8% to 10% of all lymphoma patients initially appear to have no symptoms, no obvious systemic disease. Clinical judgment is, as always, paramount. Most patients in this category have cervical lymphadenpathy. Submandibular, submental, or posterior triangle lymphadenopathy are infectious until proven otherwise. Most to be suspected as sites for lymphoma are the low cervical nodes, the nodes close to the supraclavicular areas, especially when large and anterior. Infectious or reactive nodes usually change over time. If a node in a suspected location, of one-by-one centimeter or larger, does not regress over eight weeks of observation, it should be biopsied, for one third of such lesions are proven to contain lymphoma.

A series of 285 patients staged by Henry Kaplan and associates at Stanford has been useful in indicating other nodal areas common for lymphomatous involvement. These include the axillary nodes, and, on chest x-ray, the mediastinum and the hilar areas. Spleen involvement is also common, even in the absence of splenomegaly; indeed, in such patients, up to 35% of normal-sized spleens have Hodgkin's disease on histological examination. Yet, when the spleen is normal in size and there is no evidence from noninvasive tests of paraaortic lymphadenopathy, liver involvment is extremely unusual (less than 1%). Since the spleen is properly included in radiation fields for all Stage III patients, removal is not necessary for good patient management. Strictly from a statistical view, then, in most patients the disease stage is evident for therapy purposes before laparotomy is indicated. Although surgery for diagnosis is still essential, the procedure most often should be a single-node biopsy, either external or via endoscopy.

Lymph-node biopsy is so critical for the diagnosis of lymphoma that it should be approached with some care. In a patient with multiple sites of adenopathy, the most suspicious lesions should be addressed first. That is, if a patient has an anterior cervical node and an inguinal node, the neck node should be biopsied first, unless the groin node is massively larger. In choosing between two equally suspected areas, the largest node should be taken. Crush artifact must be avoided, and a total excision is important since total nodal architecture is often important to the pathologist. In this regard, the use of frozen sections should be discouraged, as valuable tissue and architecture may be lost and a good pathologic opinion will often depend on good paraffin sections anyway.

If an exploratory laparotomy is deemed necessary, it must be approached as a systematic and formal exercise. Examination of all organs and biopsies of all abnormal sites is the first important step. Splenectomy is essential. A wedge biopsy of the right hepatic lobe and three random needle biopsies of both right and left lobes are standard. Nodal areas to be biopsied include bilateral paraaortics and iliacs, splenic, coeliac, mesenteric, and porta hepatis. All biopsied nodes should be clipped for later identification. Intraoperative x-rays may be needed to find a suspected lesion identified on preoperative LAG. A premenopausal woman should have her ovaries brought to the midline to bring them outside the "inverted Y" radiation field. Large bilateral wedge iliac bone-marrow biopsies should be obtained as well.

Clearly this is not a trivial procedure. Even in experienced hands a 12% complication rate is not unusual. Splenectomy is an important part of the procedure, even in children, in whom the risk of sepsis may approach 20%. Yet, if the surgery is indicated, it should be performed thoroughly, for an incomplete operation raises the spectre of risk without benefit.

While cure of all stages of Hodgkin's disease can be expected frequently, some patients will relapse. Total restaging is seldom indicated in these cases. Data summarized by Emil Frei III, from his cooperative group experience, has clearly demonstrated that sites of relapse most commonly involve bulky sites of original disease. Specific attention to these sites may obviate the need for compulsory restaging. For proof that will allow the discontinuation of therapy for patients entering complete remission, biopsies should involve only sites that before therapy were proven by biopsy to contain disease. This will almost never require a second laparotomy, for radiographic evidence of nodal regression is considered acceptable in this circumstance.

Non-Hodgkin's Lymphomas

The non-Hodgkin's lymphomas differ from Hodgkin's disease in many important respects. They are not orderly but skip from nodal site to nodal site without regard for anatomical pathways. Organ and bone-marrow involvement and systemic illness are common. While a true Stage I non-Hodgkin's lymphoma will rarely be found, most patients with at least contiguous nodal disease have systemic disease as well. That is, the Stages II, III, and IV are almost indistinguishable prognostically. The subclassification of non-Hodgkin's lymphomas is complex, and different pathological schemes are in current use. An attempt to develop one international formulation is at present gaining favor; this system identifies two major categories—"aggressive histology" and "favorable histology" lymphomas—of importance to the surgeon. The "aggressive histology" lymphomas include the older classification "diffuse histiocytic lymphomas" of Rappaport, other diffuse nodal variants, and nodular large-cell types. These diseases progress rapidly, are frequently widely disseminated, but respond well to treatment and may be cured with chemotherapy. The "favorable histology" lymphomas are mostly nodular in architecture or are constituted of well-differentiated lymphocytes. Some nodular lymphomas are so indolent in their course that some authors advocate no therapy until symptoms develop. The role for aggressive versus mild chemotherapy of these cases has yet to be definitively established.

Localized Stage I diffuse histiocytic or other non-Hodgkin's lymphomas are occasionally proven, and these are sometimes treated with radiotherapy alone. All other patients should receive chemotherapy, and some centers are treating Stage I patients with chemotherapy as well. A large National Cancer Institute trial, in the pre-CAT era, of 170 consecutive patients with non-Hodgkin's lymphomas explored the role of various diagnostic modalities. LAG alone led to a reclassification of a significant percentage of patients upward into Stage III. Bilateral bone-marrow needle biopsies caused some patients to be reclassified from Stage III to IV, especially in the case of the lymphocytic varieties of disease with which more than half of all patients test marrow-positive. It was the rare patient who was reclassified upward on the basis of a percutaneous liver biopsy, because other sites of involvement were already apparent in most of these cases before this procedure. Staging laparotomy resulted in minor shifts from Stage II to III and Stage III to IV. However, since only Stage I is prognostically and therapeutically distinct, almost no patient would have been mistreated had the laparotomy not been performed. Therefore, a complete work-up is indicated for seemingly early-stage diffuse histiocytic lymphomas, especially if radiotherapy alone is deemed reasonable, but laparotomy is almost never needed.

Summary

These thoughts relevant to the surgical staging of the lymphomas are not meant to be exhaustive but merely to identify issues of concern to nonsurgical oncologists. If the team approach is desirable in all aspects of oncology, it is especially vital in this field. The surgeon is involved in the most critical part of lymphoma diagnosis, the lymph-node biopsy, and should be consulted in the total evaluation of the patient. This task carries the responsibility of knowing when not to operate as well as how to operate when an operation is needed. The surgical oncologist must develop a specialized knowledge of the anatomy of lymphomas to aid other therapists in a comprehensive management plan.

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Orthopedic Oncology

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In the last decade one of the most dramatic improvements in the treatment of cancer has been in primary bone tumors. In 1973 the survival rate of those with osteogenic sarcoma was 5% to 20% and much less for Ewing's sarcoma. Through the use of chemotherapy and improved surgical techniques, we have increased the survival rate of patients with osteosarcoma to between 60% and 75%. This has allowed the use of limb-salvage procedures rather than amputation. As in all tumors, the most important initial step in treatment is accurate diagnosis. Before performing a biopsy, the clinician should have in mind the definitive future operation. It is essential that the direction of the biopsy incision be in line with the incision of any projected limb-salvage procedure. It is strongly advocated that biopsies and initial treatment be performed in the institution that is going to perform definitive treatment.

The demonstration of metastasis modifies the approach to the malignant tumor; pulmonary wedge resection in combination with total ablation has resulted in cure. Resection of pulmonary metastasis with aggressive resection of the primary malignant lesion is advocated.

Radical en bloc excision means that the surgeon stays away from the tumor, cutting only through normal healthy tissue at all times. Mistakes in technique can be fatal. By definition, *marginal excision,* or *excisional biopsy,* means that the plane of excision passes through the reactive tissue, or pseudocapsule, about the lesion. In no way can this be construed as a tumor operation. *Wide excision* means en bloc removal of the lesion surrounded by an intact cuff of normal tissue. This is an effective surgical procedure in aggressive benign tumors and low-grade malignant tumors. When dealing with highly aggressive malignant tumors, we usually require *radical resection,* that is, en bloc removal of the lesion together with the entire muscle, bone, and other tissues which are directly involved. The muscles are taken from origin to insertion. The bones are taken from joint to joint and everything that is within the compartment is removed.

Amputation is the removal of a limb or part of a limb. This may be either a marginal or a wide excision or a radical resection, depending upon the level of amputation and where the tumor is located. Amputation alone does not constitute an adequate cancer operation.

Limb Salvage

The criteria for the selection of patients for limb-salvage procedures are as follows: (a) The lesion could not be treated as effectively by radiation with or without chemotherapy; (b) There is no evidence of metastasis or the metastasis is resectable; (c) Preoperative studies indicate that the anatomic location of the lesion permits an adequate limb-salvage procedure that would be curative.

Many patients with aggressive malignant tumors are young and still growing. En bloc resections and limb salvage procedures are difficult in children younger than eight or nine because the resulting discrepancy in leg length would be more damaging than living with an amputation. Women appear to have more psychological problems with amputation than do men; however, this is of little importance as far as the decision for limb-salvage procedure is concerned. Patients who are very active do better with an amputation than with a limb-salvage procedure; they are less limited in their activities. The rehabilitation process is certainly more complex and longer with a limb-salvage procedure than with an amputation.

Preoperative studies for a limb-salvage procedure consist of whole-lung tomography or computed axial tomography (CAT) scan of the lung; liver and spleen scans; review of prior treatments

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and histologies; tomograms, a bone scan, angiography, and a CAT scan of the involved area. The angiogram and the CAT indicate whether a limb-salvage procedure is feasible. Arterial grafting is frequently chosen in preference to freeing the artery and jeopardizing the limb. However, it is impossible to do a satisfactory limb-salvage procedure if the sciatic nerve or a major nerve has to be sacrificed. It is of no value to leave the patient with an insensate or nonfunctioning limb.

Amputation is favored when a local resection results in an inadequate margin of removal, excessive limb shortening, paralysis, complete instability of the limb, or anesthesia in the limb. As a palliative procedure, an amputation is preferred to avoid a long convalescence.

Twenty-three patients at The Mount Sinai Medical Center underwent limb-salvage procedures from 1974 to 1982. The results are very gratifying for most patients; only one patient has died; another had recurrent disease and had to undergo another resection of the tumor. Two patients had to undergo subsequent amputations following failure of the limb-salvage procedure.

Case Reports

Case 1 is a 16-year-old boy with osteogenic sarcoma involving his proximal tibia. The arteriogram showed that the major vessels were spared by the tumor. The patient's proximal tibia was resected; his popliteal artery was replaced with vein graft. The sciatic nerve was spared. A metallic rod was placed into his femur through the greater trochanter and passed down the marrow cavity and into the marrow cavity of the tibia down to the ankle. A graft from the femur was placed across the resected section of the knee. His fibula was resected and this was also used as a graft to span the resected section of the knee. Additional bone graft was taken from the iliac crest. The patient has healed across the resected area. He can walk bearing full weight, with a stiff knee from the fusion. He has done well, being free of disease some two years after this procedure was completed.

Case 2 is a 13-year-old girl with osteogenic sarcoma involving the distal femur. Bone scan showed the entire distal femur was involved. CAT scan showed soft-tissue involvement that required the removal of the entire quadriceps mechanism along with the entire femur. The resected specimen showed that the entire tumor was removed, with an adequate cuff of normal tissue. It is fortunate that the entire femur was removed; examination of the specimen showed a skip area within the marrow cavity of the femur significantly above the upper margins of the original osteogenic sarcoma. For many years pathologists did not believe that skip areas occurred in osteogenic sarcoma. The literature now substantiates its occurrence. Had an amputation been performed on this young lady, the skip area would probably have been left behind. It is customary to perform the amputations seven inches above the upper margins of the tumor as seen on CAT scan. A retrospective review of the preoperative CAT scan failed to show this skip area. The patient underwent a total femur replacement with a new hip, new knee, and an entire metal femur. She is doing very well. She walks with absolutely no support and has only a minor limp that is discernible only when she is carefully observed.

Case 3 is a 15-year-old boy with Ewing's sarcoma of his femur who had undergone radiotherapy and chemotherapy, then sustained a pathologic fracture of his femur. In the past, pathologic fractures necessitated amputation of the limb because of the failure of these fractures to heal. In this case, instead of amputating the femur, a total femoral replacement was performed. He also has done dramatically well. He walks without mechanical aid and with a slight limp. He is able to go bowling and functions normally in nonathletic activities.

Prostheses

At the Mount Sinai School of Medicine, there is a preference for the use of custom-made prosthetic replacements when dealing with limb-salvage procedures involving the long bones. Allografts have also been used on a number of occasions. Although the literature reports a very high complication rate with the use of allografts in tumor surgery, the complication rate with custom-made prostheses appears to be much smaller. We use a surgical operating room equipped with a laminar flow machine when working with custom-made prostheses for limb salvage procedures. Great care is taken to place these prostheses under highly aseptic conditions.

Preoperative chemotherapy to prevent the spread of disease is used in all of our limb-salvage procedures because 4–6 weeks is necessary to obtain the custom-made prosthesis. Considerable shrinkage of the tumor is often seen following this chemotherapy.

Limb-salvage procedures have proved effective in the treatment of malignant tumors of bone. The results compare favorably with amputation. New procedures in prosthetic manufacture and techniques will continue to improve the results.

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Conservation Surgery of the Larynx

Hugh F. Biller, M.D.

Conservation surgery of the larynx is not conservative surgery. Conservation surgery is a radical concept in which areas of the larynx are resected and reconstructed with maintenance of the respiratory, phonatory, and protective functions of the larynx. Conservation surgery can be performed without sacrificing curability as compared to total laryngectomy.

The ability to perform partial laryngeal surgery requires a knowledge of the biologic behavior of that particular carcinoma and the ability to reconstruct following the extirpative surgery. The area of tumor involvement determines what has to be excised. The reconstruction of the larynx following tumor resection remains extremely difficult, and most decisions for total laryngectomy are related to the inability of the surgeon to reconstruct the larynx. Since our ability to reconstruct the larynx continues to improve, the limitations of partial laryngectomy are changing. As new reconstructive techniques become more sophisticated, partial laryngeal surgery will become more feasible.

Glottic Cancers. Tumors of the vocal cord that extend beyond the confines of the membranous cord to involve either anterior commissure, subglottis, or arytenoid have the best chance of cure with surgery. These tumors are treated by the classical vertical partial laryngectomy (hemilaryngectomy) (1). Glottic tumors which demonstrate fixation of the vocal cord respond poorly to radiotherapy and are treated by surgery. The procedure employed has been total laryngectomy. Classical hemilaryngectomy gives inadequate results, with a 50% incidence of local recurrence. The classical procedure does not allow for an adequate margin subglottically. A partial procedure that would be adequate would require resection of the upper border of the cricoid cartilage. It has been our experience that adequate tumor control is obtained in these tumors if the hemilaryngectomy procedure is extended to include the cricoid cartilage. Reconstruction following this type of resection is performed by utilizing the posterior border of the thyroid cartilage pedicled on the inferior constrictor muscle (2). The reconstruction enables the patient to be rehabilitated without aspiration and with an adequate airway and adequate voice.

Supraglottic Cancers. Cancers of the epiglottis involving only the suprahyoid portion are adequately controlled by radiotherapy. Cancers which involve the infrahyoid portion of the epiglottis are inadequately treated by radiotherapy. These tumors rapidly invade the pre-epiglottic space and exhibit a biologic behavior that responds poorly to radiotherapy. Surgery, on the other hand, yields an excellent rate of tumor control. These tumors, provided they are limited to the supraglottis and do not show evidence of glottic involvement anteriorly, rarely involve cartilage and are amenable to a horizontal partial laryngectomy (supraglottic resection). The rehabilitation is enhanced by performing a cricopharyngeal myotomy. Inability to decannulate the patient is rare and persistent aspiration is unusual. Perfect glottic closure is required for rehabilitation of deglutition. This necessitates arytenoid replacement and midline vocal-cord fixation in cases where the arytenoid cartilage is resected. It also requires accurate postoperative evaluation and subsequent procedures to obtain glottic closure if glottic closure is inadequate (3).

Select supraglottic tumors which extend inferiorly to cross the ventricle and involve the true vocal cord can also be treated by partial laryngectomy. This type of resection involves a combination of a hemilaryngectomy with a supraglottic laryngectomy (three-quarter partial lar-

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yngectomy). The larynx is reconstructed by utilizing the posterior border of the thyroid cartilage pedicled on the inferior constrictor muscle (4). This allows the formation of a pseudocord, thereby permitting glottic closure. The neocord is covered on its superior and inferior surfaces by a pedicled mucosal graft from the pyriform sinus.

The performance of partial laryngeal surgery requires a thorough anatomical and physiological understanding of the larynx. As our reconstructive efforts improve, larger resections will be performed. Theoretically, the only unit that need remain following a resection is one mobile arytenoid. This means that in principle a resection including the epiglottis, false cords, entire thyroid cartilage, both vocal cords, and one arytenoid and one-half of the cricoid cartilage could be done, if a technique of reconstruction could be devised. From our past experience, this type of reconstruction is possible and will be accomplished in the future.

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Tumor-Associated Immunity and Serum Blocking by Radioisotopic Leukocyte Adherence Inhibition Assay

P. H. TSANG, PH.D., JAMES F. HOLLAND, M.D., AND J. GEORGE BEKESI, M.D.

In vitro assays of cell-mediated immunity have played an important role in the study of antitumor responses in human cancer and of factors modifying their expression. Assays such as blastogenesis (1–3), migration inhibition (4, 5), and cytotoxicity (6–9) are time consuming and often difficult to interpret. In our search for a sensitive and reproducible technique for measurement of cell-mediated immunity in cancer patients, we have developed a modification of the leukocyte adherence inhibition (LAI) assay employing radioisotope-labeled leukocytes (10).

This assay is based on the original observation of Halliday and Miller that the glass adherence of peritoneal leukocytes from tumor-bearing mice was reduced in the presence of a corresponding syngeneic tumor extract (11). In the original method, Halliday incubated mixtures of leukocytes and antigens in hemocytometer chambers. The degree of LAI was determined by counting the residual glass-adherent cells after gentle washing (11). Subsequent attempts to simplify this technique include Thomson's tube method and Holt's microplate method (12, 13). In the tube method, mixtures were incubated in glass tubes and the nonadherent cells remaining in the fluid were counted in hemocytometers (12). Holt incubated cells and antigens in plastic tissue-culture plates (13). Observers using Halliday's and Holt's methods proposed that the adherence of leukocytes was reduced by a soluble factor produced by sensitized T cells in response to specific tumor extracts (9, 10). In contrast, Thomson's group supports a mechanism involving arming of indicator monocytes by cytophilic antibodies or soluble immune complexes (11, 12). They also reported a tumor eclipse phenomenon related to high circulating levels of blocking factor in advanced cancer patients, resulting in abrogation of LAI response (14, 15). The ability of LAI assay to correlate high levels of blocking factor with tumor progression can have prognostic value in evaluation of immunocompetence and in assessment of residual tumor burden during treatment. It also suggests that removal of blocking factor may have therapeutic applications by restoring the immunocompetence of these patients.

In our radioisotopic modification of the LAI assay, purified peripheral blood leukocytes (PBL) were prelabeled with ^{51}Cr-Na$_2$CrO$_4$ prior to incubation with allogeneic tumor extracts in the presence of normal AB serum or autologous serum. Compared to methods based on visual counting, this LAI assay is less technically demanding and is less sensitive to observers' variation. Furthermore, what is analyzed is the entire population of PBL in each tube, rather than representative samples chosen at random from a microscopic field.

Essential steps in the development of this assay were the standardization of conditions for optimal ^{51}Cr uptake by PBL and the inclusion of autologous or normal AB serum in the incubation media. A dextrose salt solution was found to enhance intracellular uptake of ^{51}Cr significantly (eightfold), without loss of viability of the cells and without selective loss of specific subpopulations. The higher intracellular uptake of ^{51}Cr by PBL minimizes the counting error and the variance between individual points in each set of triplicates and thereby improves the accuracy of the

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assay. The presence of 10% autologous or AB plasma was absolutely essential in order to avoid nonspecific LAI responses to unrelated normal tissue and tumor antigens. In our preliminary studies, (1, 16, 17), patients with operable breast cancer have been successfully distinguished from those with benign breast tumors and from patients with other types of cancer. To further evaluate the diagnostic value and the effect of tumor burden and circulating serum factors on the tumor-host relationship, LAI testing was expanded in the present study to include patients with more advanced cancer.

Subjects, Materials, and Methods

Patients. A total of 112 breast-cancer patients were studied, without selection; all patients who came to The Mount Sinai Hospital for surgery or treatment during a two-year period were included, after informed consent was obtained. The clinical-pathological staging (TMN classification) was as follows: Stage I (local tumors), 27 patients; Stage II (involvement of regional nodes), 43 patients; and Stage IV (distant metastasis), 42 patients. All these patients were studied prior to any chemotherapy or radiotherapy.

Control subjects consisted of 61 healthy women donors to the blood bank. In addition, 29 patients with benign breast diseases, 25 patients of both sexes with colorectal carcinoma, and 10 patients with melanoma were studied. Diagnosis was not available at the time of assay, and the test was conducted without knowledge of the diagnosis.

Sera. Autologous serum was obtained from each subject by allowing peripheral blood to coagulate. Within 2 hours, it was then centrifuged at 400 × g for 20 min. Human AB pooled serum was obtained from North American Biological Inc. All serum samples were decomplemented at 56°C for 45 min.

Leukocyte Purification and Labeling. As described previously (1), peripheral blood was drawn in a heparinized (10 units of preservative-free heparin/ml of blood) plastic syringe. Leukocytes were isolated on a Ficoll-Hypaque gradient (Pharmacia Fine Chemicals) and centrifuged for 45 min at 1000 × g at 20°C. The mononuclear cells located at the interface of the gradient were collected, washed 3 times with phosphate-buffered saline, and resuspended at a concentration of 2×10^7 cells/ml in a glucose-saline solution (GNK, 1 g dextrose, 4 g potassium chloride, 9 g sodium chloride per liter of triple distilled water, pH adjusted to 7.4). Leukocyte labeling was performed as follows: ^{51}Cr as sodium chromate with specific activity of 350–500 μCi/μg (New England Nuclear, Boston, MA). Purified PBL were suspended in polyallomer tubes (Beckman) in the presence of 200 μCi of ^{51}Cr in a Dubnoff water bath at 37°C, while shaking at rate of 100 cycle/min for 45 min. After incubation, labeled lymphocytes were washed three times with 40 ml of ice-cold GNK and resuspended to a final concentration of 1×10^6 ml in RPMI-1640 plus 10% autologous or AB serum.

Chromation performed in polyallomer tubes yielded only a 3.9% loss of cells, compared to 37.4% and 42.1% in plastic and glass tubes. Microscopic examination of PBL before and after labeling with ^{51}Cr showed no alteration in composition in subpopulation of lymphocytes. Average number of T cells, as determined by the fluorescence-labeled, monoclonal antibody staining method, was 67.1%; of B cells, 19.2%; of monocytes, 18.5%. The total incorporation of ^{51}Cr with PBL was repeatedly observed at 19,000 ± 1,800 cpm/10^5 lymphocytes as determined in a thallium-activated sodium iodide well-type gamma counter (Packard Instrument, Downer's Grove, IL). Viability of labeled lymphocytes, as determined by the trypan blue dye exclusion test, was consistently not less than 98%.

Preparation of Tumor Extracts. Tumor extracts were prepared aseptically as previously described (1, 16, 17), using freshly obtained primary tumors, except in colorectal cancer where metastatic deposits from patients with invasive specimens were used.

Briefly, after tumor tissues were trimmed free of fat and necrotic tissues, they were cut up fine with scissors, passed through a steel mesh screen, and treated with collagenase (2 mg/gm tissue weight). The single cell suspension thus derived was washed twice with GNK to remove the enzyme, and then ruptured with 50 strokes of a loose fitting Dounce homogenizer. This procedure disrupted 90% of the cells but left nuclei largely intact, as determined by phase contrast microscopic examination. The cell lysate was then centrifuged at 1000 × g for 10 min at 4°C to remove intact cells and nuclei. The supernatants were collected and centrifuged on a discontinuous sucrose gradient (40%–60%) at 90,000 × g for 2 hours to isolate plasma membrane particulates from mitochondria, endoplasmic reticulum membranes, and ribosomes. The interfacial bands were obtained, and the protein content was determined (18, 19) and adjusted to give a final protein concentration of 2–5 mg/ml.

Experience has shown that not all tumor antigen preparations have the capacity to evoke tumor-specific responses. Accordingly, the tumor antigens were tested for activity and cross-reactivity, using the LAI assay to determine whether it brings about tumor-specific inhibition of leukocyte adherence when incubated with leukocytes from patients known to have a cancer of the same histological origin. Those extracts demonstrated to be active were stored at −196°C. Just prior to LAI testing, tumor extracts were thawed and centrifuged at 1000 × g for 10 min before being assayed.

^{51}Cr-LAI Assay. The procedure for assay is outlined in Fig. 1. We used labeled PBL, either in RPMI-1640 + 10% AB serum, or in RPMI-1640 + 10% autologous serum, at concentration of 1 × 10^6 cells per ml. Aliquots of 100 μl of the leukocyte suspension 10^5 cells were seeded in polyethylene tissue culture tubes (NUNC, 13 × 100 mm) by using a Hamilton dispenser. Equal volumes of various dilutions of normal or tumor antigen extracts (100 μg/tube) in RPMI-1640 were added. After mixing, leukocytes were incubated at 37°C for 2 hours in a humid atmosphere with 5% CO_2. All assays were performed in triplicate. At each experimental point, a fourth tube was incubated in the same manner. After incubation, this fourth tube was centrifuged, supernatant removed, and the free ^{51}Cr determined. In all cases, 20%–25% of the incorporated radioactivity was found to be released spontaneously during the 120-minute LAI incubation. This was taken into account in the calculation of LAI by subtracting the background value of spontaneous release from the total observed value of radioactivity. The net radioactivity would then represent the corrected experimental value under the conditions employed.

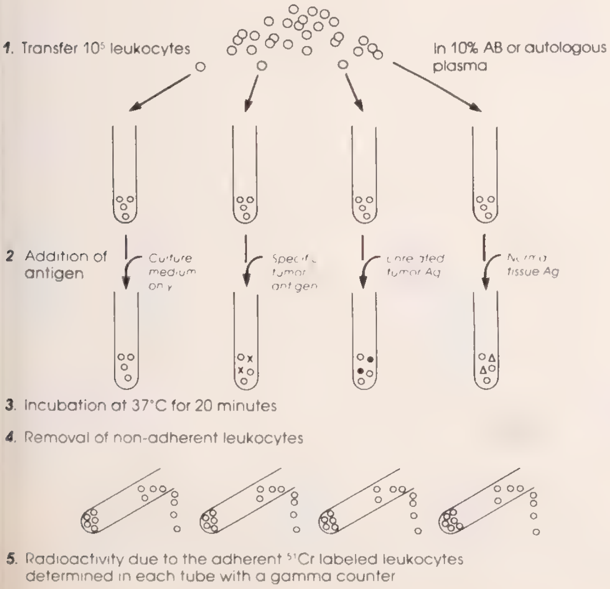
1. Transfer 10⁵ leukocytes
In 10% AB or autologous plasma
2 Addition of antigen
Culture medium only
Specific tumor antigen
Unrelated tumor Ag
Normal tissue Ag
3. Incubation at 37°C for 20 minutes
4. Removal of non-adherent leukocytes
5. Radioactivity due to the adherent ⁵¹Cr labeled leukocytes determined in each tube with a gamma counter

Fig. 1. ^{51}Cr leukocyte adherence inhibition assay.

Evaluation of Results. The mean counts per minute (cpm) and SE were computed for each group of triplicate tubes. In each subject to be tested, a baseline of normal adherence in RPMI-1640 medium with 10% autologous or AB serum in the absence of antigenic extracts was established. These values compared to corresponding values for mixtures containing antigen and the degree of responsiveness in percent was expressed by the following method:

$$\mathrm{LAI} = \frac{A - B}{A} \times 100$$

where A = mean cpm of adherent cells without antigen after correction for spontaneous release, and B = mean cpm of adherent cells with antigen after correction for spontaneous release.

Serum blocking effects of autologous serum in the LAI reaction is expressed in the equation

$$\%\ \mathrm{SB} = 1 - \frac{\%\ \text{LAI of PBL incubated with autologous serum}}{\%\ \text{LAI of PBL incubated with normal AB serum}}$$

where %SB = percent serum blocking.

An analysis of variance was performed on the mean LAI (%) indexes between the various subject groups and significant differences were specified according to Kramer's extension of Duncan's New Multiple Range Test.

Results

Prevention of Nonspecific LAI Responses. The presence of 10% AB serum in the incubating mixture was absolutely essential in avoiding nonspecific LAI reaction against normal and unrelated tumor extracts. This was illustrated in the first series of experiments, in which labeled leukocytes from breast cancer patients (Stages I and II) and normal controls were incubated with different concentrations of breast-cancer antigens or benign-breast-tissue extracts in serum-free medium or in medium containing 10% AB serum. LAI percentage was determined after 2 hours incubation. In the absence of serum, there was a strong nonspecific LAI response to both tumor antigen and benign-breast-tissue extracts by both breast cancer patients and healthy donors (Fig. 2). On the other hand, in the presence of normal AB serum, LAI response was evident only with PBL of breast-cancer patients. The optimal antigenic concentration for this specific reaction ranged from 50 to 150 μg per tube. Under that condition,

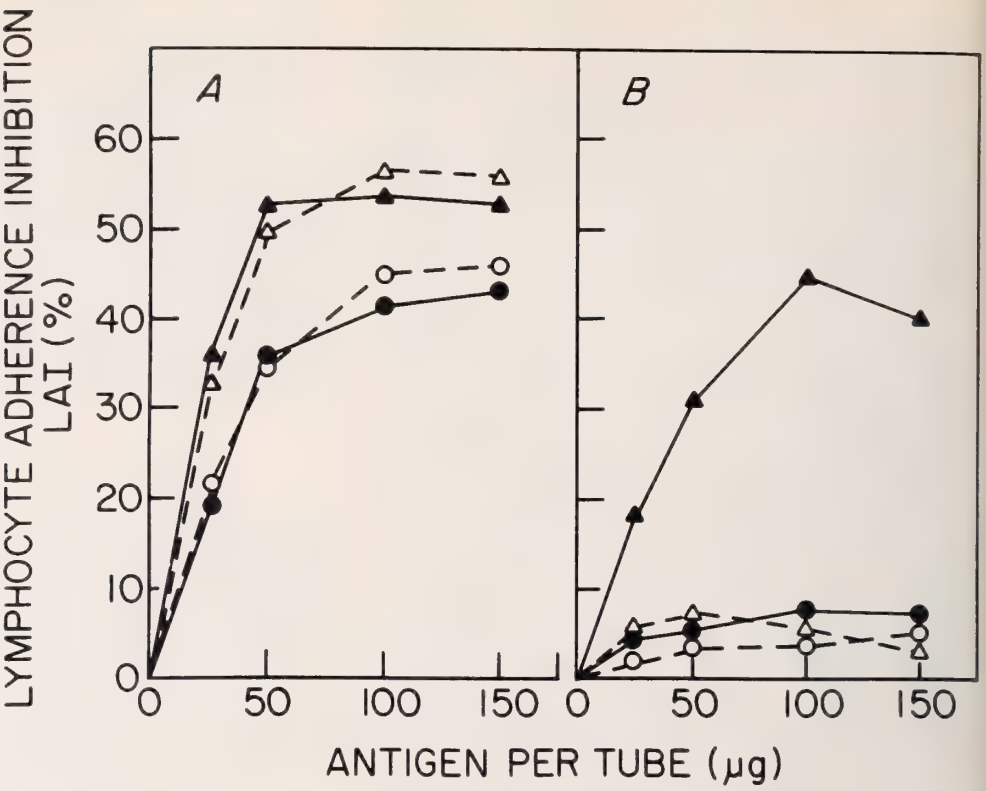

Fig. 2. Human AB serum prevents nonspecific LAI responses. ▲, breast cancer patients with breast cancer antigen; △, normal subjects with breast cancer antigen; ●, breast cancer patients with benign breast tissue antigens; ○, normal subjects with benign breast tissue antigens.

LAI values ranged from 30% to 45% in patients with Stage II breast cancer and less than 10% for normal subjects.

Predictive Value of LAI. A positive LAI response was defined as one that showed more than 18% inhibition of adherence. This value was derived by taking the 95 percentile of LAI index obtained from 61 normal control subjects in response to breast tumor extracts in the presence of AB serum. In a study of 73 preoperative patients with suspected breast cancer, accurate prediction of the presence of cancer was achieved (Fig. 3). The PBL of all patients with localized breast tumor showed significant adherence inhi-

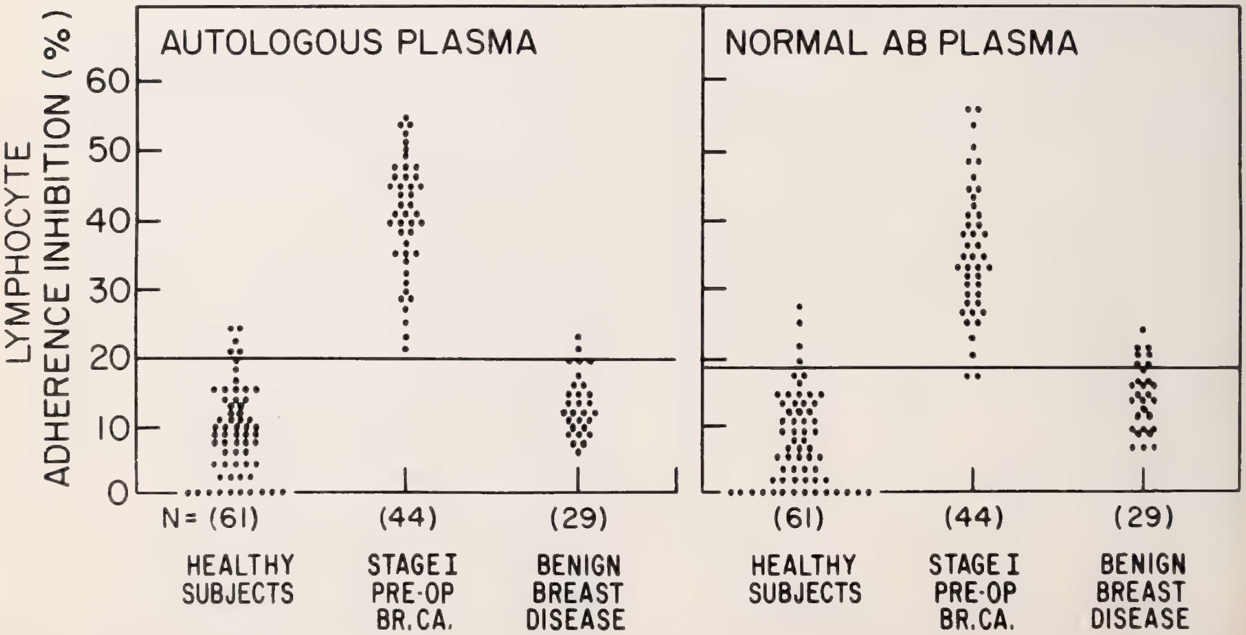

Fig. 3. Leukocyte adherence inhibition reactivities in response to breast tumor extracts among various groups of patients and controls.

TABLE

Specificity of LAI Reaction with 3 Different Tumors

Sources of PBL	Benign breast disease % LAI ± SD (response*)	Breast CA % LAI ± SD (response*)	Melanoma % LAI ± SD (response*)	Colon CA % LAI ± SD (response*)
Breast CA	4.3 ± 2 (0/19)	40.4 ± 4 (27/27)	8.2 ± 3 (1/12)	8.5 ± 3% (2/14)
Melanoma	5.4 ± 3 (0/10)	4.5 ± 3 (1/12)	36.3 ± 5 (8/10)	9.2 ± 3% (1/11)
Colon CA	5.9 ± 4 (0/25)	8.2 ± 3 (2/25)	5.2 ± 4 (0/25)	29.2 ± 5 (22/25)

* Number of patients responded/number of patients tested.

bition in response to allogeneic breast-tumor extracts (mean 41.2 ± 9%), whereas the PBL of normal control women and of patients with benign diseases did not respond (mean LAI 11.3 ± 4% and 12.5 ± 5% respectively). Neither the PBL of patients with cancer nor of those with benign diseases reacted to benign-breast-tissue extracts, thus ruling out the possibility of nonspecific response to normal organ-specific antigen. The predictivity of breast cancer in tested patients was 95% (42/44); false positive results in normal subjects were <5% (3/61).

The specificity of ^{51}Cr LAI assay in detection of homologous tumor antigen by sensitized leukocytes was further demonstrated in a series of experiments in which labeled PBL from patients diagnosed to have breast carcinoma (Stages I and II), colon cancer, and melanoma were exposed to antigens prepared from their tumors. Leukocytes of all breast cancer patients (N = 27) reacted to breast-tumor antigens but minimally to melanoma and colon cancer extracts (Table).

Tumor specificity against the respective tumor antigens was also demonstrated in patients with melanoma and colon cancer. The melanoma antigens were recognized by the PBL of melanoma patients but not by colon-cancer patients. Similarly, colon-cancer antigen elicited responses of leukocytes of colon-cancer patients but none in those of melanoma patients.

Demonstration of Blocking Factor. To evaluate the effects of tumor burden on antitumor immunity, LAI testing of cell-mediated immunity was expanded to include patients with more advanced breast cancer. Figure 4 summarizes the response to breast-tumor antigen in the presence of normal AB serum by three groups of breast cancer patients at various clinical stages of their

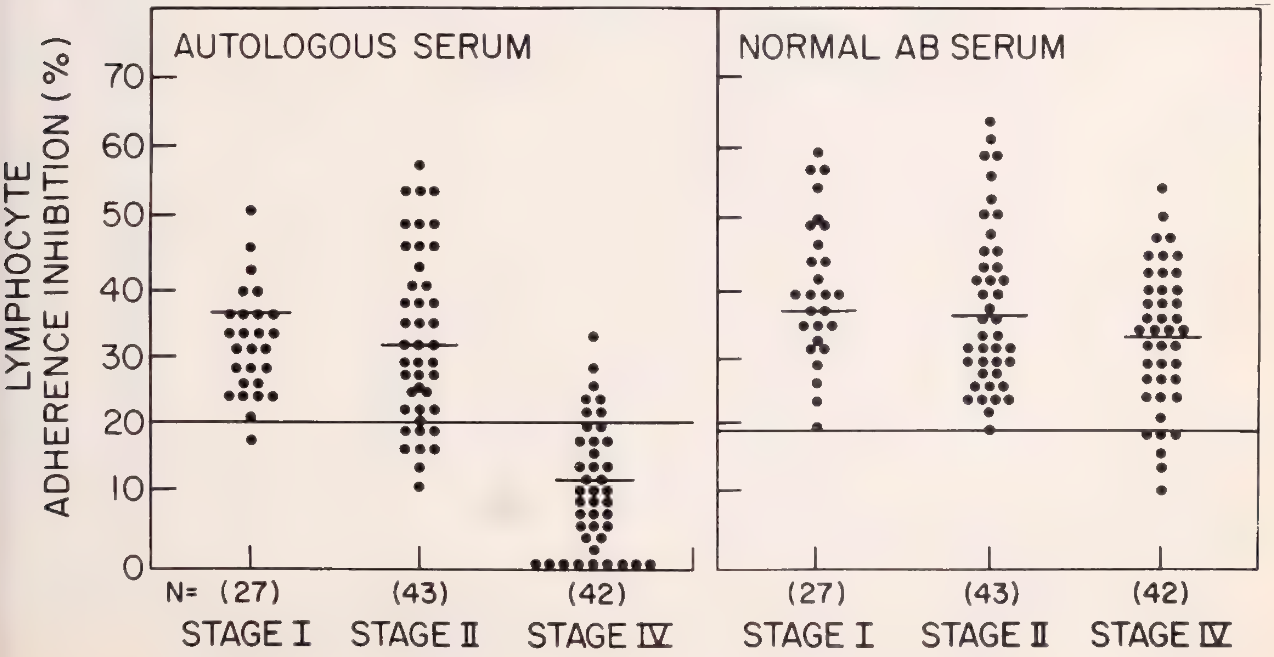

Fig. 4. Response to breast tumor extracts by various groups of breat cancer patients.

neoplasm. The groups studied include 27 patients with Stage I breast carcinoma, 43 with Stage II, and 42 patients with Stage IV. The results show very little difference between the LAI response and tumor burden when the assay was performed in normal AB plasma, although the LAI index appears to be slightly lower in subjects with advanced disease. The mean LAI of these three groups were 37.2 ± 6%, 36.6 ± 5%, and 30.8 ± 6% respectively. Taking 18% inhibition of adherence as the cut-off point as previously described, 6 of 42 Stage IV patients were identified as being LAI-negative.

To demonstrate serum blocking of LAI reactivity, labeled PBL from these patients were incubated in 10% autologous serum instead of normal AB serum. In Stage I and II patients, no abolition of LAI response by the patients' own serum was observed (mean LAI index was 36.3 ± 7% and 32.4 ± 8% respectively). By contrast, using serum of patients with Stage IV breast cancer, the mean LAI index was reduced to 10.8 ± 5%. A correlation between blocking factor and tumor burden of breast cancer was positively established when the blocking indexes were compared (Fig. 5). The serum of 39 of 42 patients with Stage IV disease showed blocking index values of more than 0.4, whereas only 1 of 27 Stage I patients and 8 of 43 Stage II patients tested positive for blocking index.

Discussion

Essential steps in the development of the ^{51}Cr LAI assay were the standardization of conditions for optimal radioisotope uptake by peripheral blood leukocytes and the inclusion of autologous or normal AB serum in the incubation medium. In both respects, this procedure is different from some of the earlier LAI methods described. The use of ^{51}Cr-labeled PBL alleviated subjective errors introduced by visual counting, while the presence of normal AB serum prevented nonspecific LAI responses to unrelated tumor antigen in our assay system. The necessity for having serum in the incubation medium has been discussed by Halliday (20). He postulated that LAI involves a reaction between committed T lymphocytes and antigen, leading to the production of an inhibitory factor (LAIF) which in turn renders other leukocytes nonadherent. Normal AB serum prevents enzymatic destruction of this lymphokine. The tube-LAI assay performed by Thomson (21), on the other hand, appears to involve a direct reaction between monocytes carrying cytophilic antibody and tumor antigen and may proceed best in the absence of serum. In view of these differences, it is not surprising that our results were quite different from those reported by others.

The predictive and discriminatory power of the

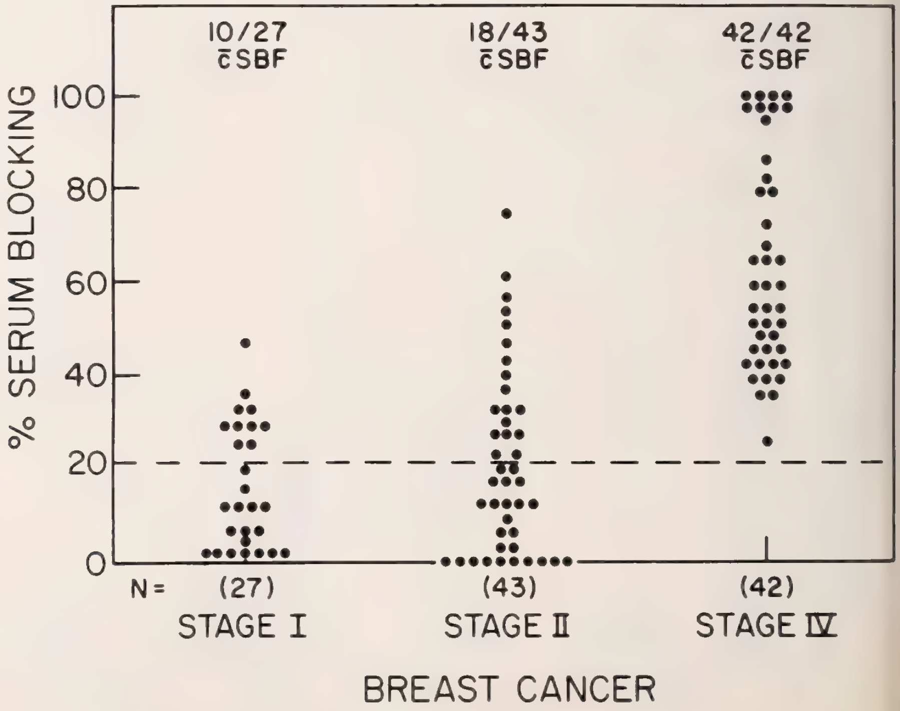

Fig. 5. Percentage serum blocking in response to breast tumor extracts by various groups of breast cancer patients. c̄ SBF: leukocyte adherence inhibition assay demonstrated presence of serum blocking factor.

radioisotopic LAI assay may be gauged from the results of our clinical studies in preoperative cancer patients. ^{51}Cr assay performed on purified PBL in normal AB human serum was able to discriminate between tumors of different histological types of sites of origin. All patients with tumors other than the specific types assayed gave a negative LAI reaction to that particular tumor antigen. In double-blind studies this assay was able to distinguish effectively between patients with carcinoma in its early stages from those with benign diseases. In light of these findings, the ^{51}Cr LAI assay provides us with a powerful tool in making differential diagnoses in patients with early stages of cancer.

For evaluation of the effects of tumor burden on host immunity, LAI testing was performed on breast-cancer patients in more advanced stages of tumor progression. In the presence of normal AB serum, LAI reactivity was not strikingly decreased for patients with Stage IV diseases. This was contradictory to Thomson's report of eclipsed phenomenon in 73 of 103 breast-cancer patients (14). The higher percentage of positive LAI response in our study can be explained by unmasking, due to additional washing steps during chromation procedures, those receptor sites on patients' leukocytes which had been neutralized by excess circulating tumor antigens. This theory was supported by Yonemoto's (22) observation that more than one half of LAI-negative patients could be converted to positive LAI following six additional washings of leukocytes. Powell (23) also observed that in cytoxicity assay, following additional washings there was a progressive increase in the cytolytic effect of patients' lymphocytes on the target cells.

Since ^{51}Cr LAI assay performed in normal AB serum did not indicate whether the patient was free of cancer, it is of minimal value in monitoring patients undergoing treatments. However, when autologous serum of the patient was used in the assay, presence of blocking factor(s) was correlated with tumor progression or residual tumor. In clinical applications, this observation is potentially very useful in long-term followup of patients after treatment. The ^{51}Cr LAI assay must, therefore, be performed in the presence of both AB serum and patient's autologous serum to fully exploit its potential.

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Immune Complexes in Cancer and Preneoplastic Diseases

MICHAIL SHAFIR, M.D.

Dr. Bekesi of this institution has been my master in tumor immunology for quite some time and has got me interested in looking into a collateral aspect of some of the work he has presented.

A few years ago we performed studies on patients with colorectal cancer and investigated what happened to several of their immune parameters before the surgery and six to eight weeks after the surgery; we saw a few interesting things (1). For instance, when we studied the reactivity of the patients' lymphocytes preoperatively as compared to postoperatively, we specifically looked at the differences resulting from incubation with autologous serum as opposed to incubation with allogeneic normal serum. We observed that with the autologous serum, most of the patients had a lower lymphoblastogenesis transformation rate; this applied to all stages of the disease, suggesting that something was happening in the serum of these patients in the autologous setting that was probably blocking this activity (Figs. 1, 2). And so, based on the extensive work suggesting that the "blocking factor" is most probably represented by circulating immune complexes, and because of solid evidence that several conditions in the intestine are clearly preneoplastic (especially longstanding inflammatory bowel diseases), we are studying these immune complexes and characterizing them in patients with cancer, inflammatory bowel diseases, and cancers other than colorectal. We are trying to answer the question of whether immune complexes can be used as markers and help in predicting neoplastic transformation. I don't think we are near answering that question yet, but we are on the way.

To study immune complexes, we draw venous blood, spin it down, incubate it, and then precipitate it with polyethylene glycol, following a modification of Creighton's method (2). This yields a pellet that mainly consists of immune complexes (Fig. 3). We saw that in patients with colorectal cancers, although we did not divide them in this study by stages, quite a few results were clearly above the normal range. We studied a few patients with ulcerative colitis, and we found that they all were above the normal range; and in Crohn's disease, they were mostly above as well. Although the samples were small, it did seem that with respect to immune complexes, there was quite a difference between colorectal cancer, ulcerative colitis, and Crohn's disease versus normal (Fig. 4).

Immunoglobulins. As the study continued, we tried to identify which immunoglobulin was responsible for the constitution of these immune complexes. We saw that immunoglobulins A, G, and M were at much higher than normal levels in the circulating immune complexes of patients with inflammatory bowel disease and colon cancer, independently of the nature of the process (Fig. 5).

In our initial study of colorectal cancers, we saw an elevation of free immunoglobulins postoperatively, suggesting that once the tumor was removed, immunoglobulins that may have been attached to or involved with the tumor became freely available, or that the immunoglobulins continued to be produced but instead of getting trapped in the tumor started circulating freely in the peripheral blood. Again, this suggested that in neoplastic patients there is a local immunological response.

In an attempt to confirm this to some extent,

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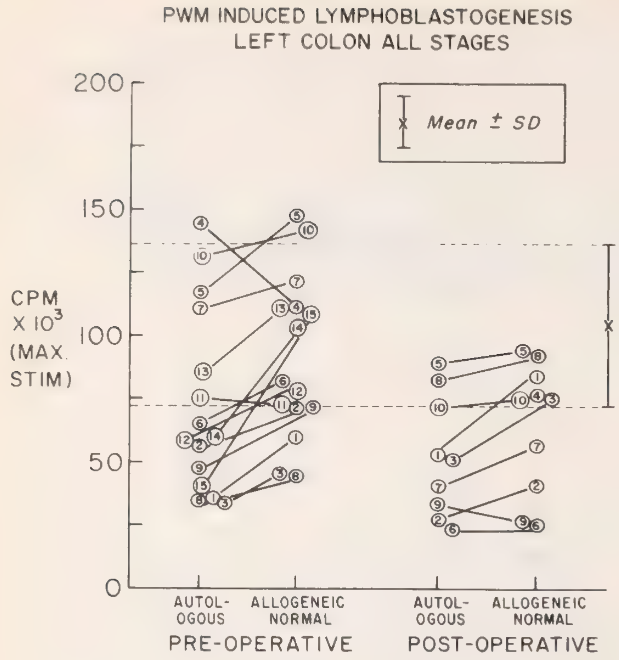


Fig. 1.

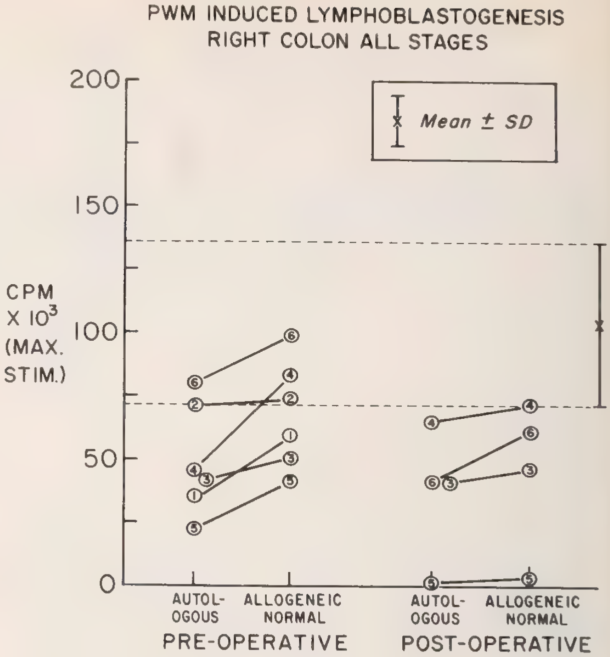


Fig. 2.

we took the tissues of the resected specimens from patients with colon cancers, and we looked at the extracts of the tumors and the extracts of the edges of the resection of what appeared to be normal mucosa. We found that IgG, mainly, and IgA as well were significantly higher in the tumor extracts as compared to the normal tissue. We could not detect IgM in either.

PEG ASSAY METHODOLOGY

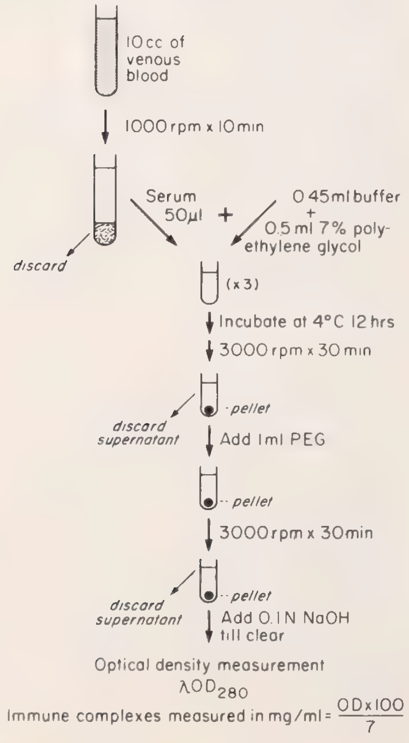

10cc of venous blood
1000 rpm x 10 min
discard
Serum 50µl
+
0.45 ml buffer + 0.5 ml 7% polyethylene glycol
(x3)
Incubate at 4°C 12 hrs
3000 rpm x 30 min
discard supernatant
pellet
Add 1ml PEG
pellet
3000 rpm x 30 min
discard supernatant
pellet
Add 0.1 N NaOH till clear
Optical density measurement
λOD280
Immune complexes measured in mg/ml = $\frac{OD \times 100}{7}$

Fig. 3. Left PEG assay methodology.

RESULTS

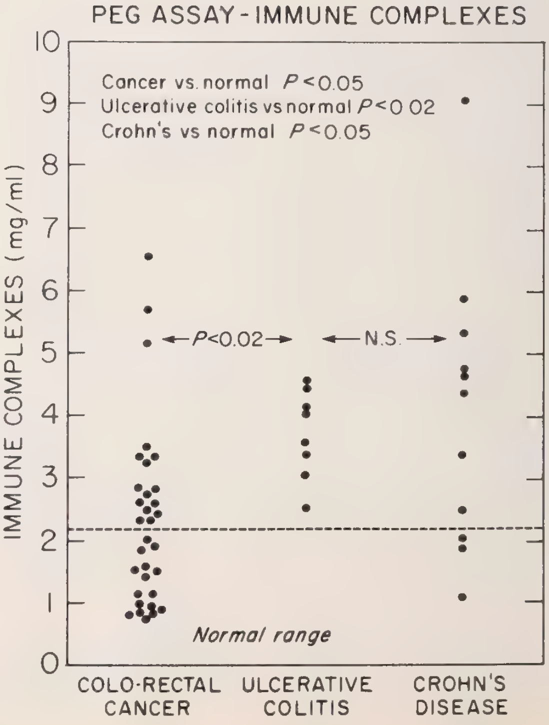


Fig. 4. Right.

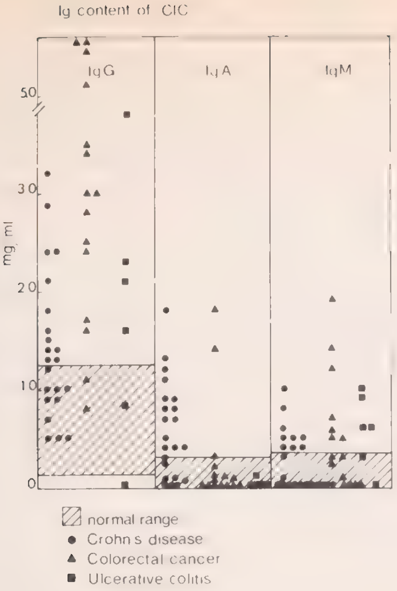


Fig. 5.

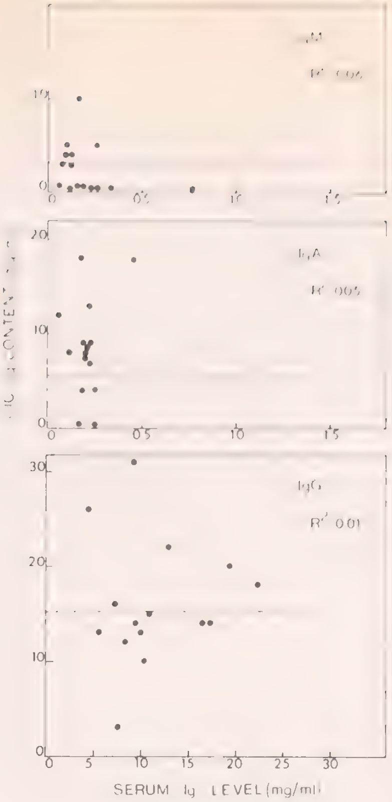
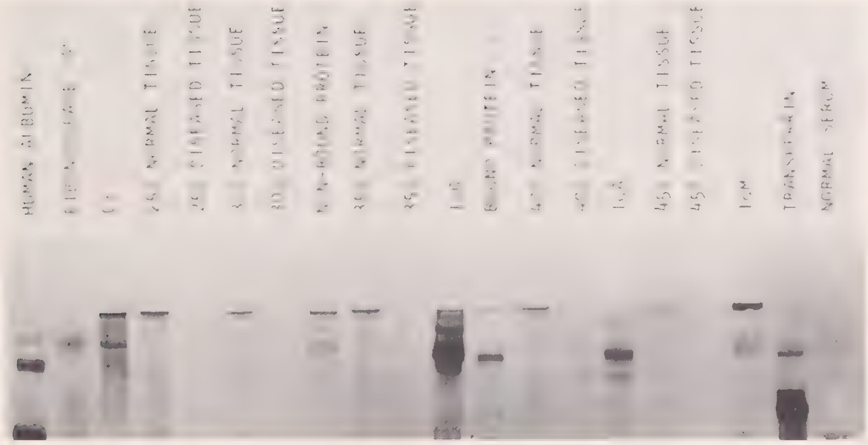


Fig. 6.


HUMAN ALBUMIN
NORMAL TISSUE
DISEASED TISSUE
NORMAL TISSUE
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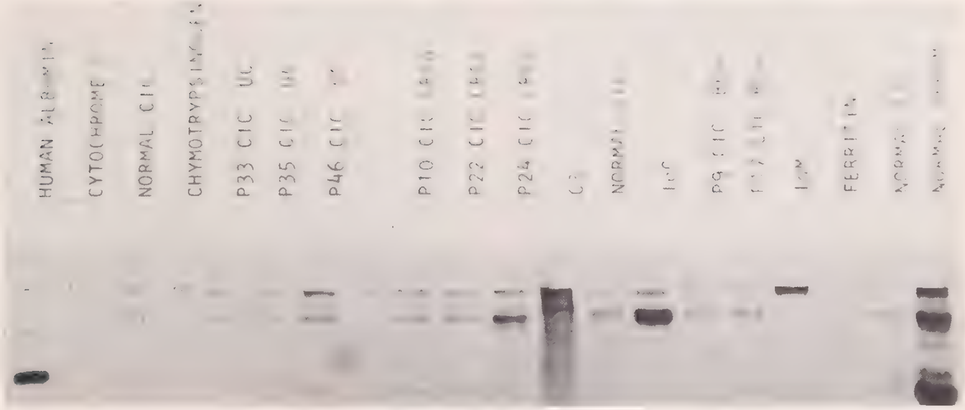
TRANSFERRIN
NORMAL SERUM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P46 CIC
P10 CIC
P22 CIC
P24 CIC
NORMAL
IgG
IgM
FERRITIN
NORMAL
NORMAL

Fig. 7. Bottom SDS-Page: Circulating immune complexes (CIC) of patients with ulcerative colitis (UC), colorectal cancer (CR Ca), and breast cancer (B Ca).

Fig. 8. Top SDS-Page: Crohn's disease patient, normal and diseased tissue after centrifugation on sucrose gradient (* = circulating immune complexes of the same patient after chromatography on Protein A-Sepharose CL 4B).

Going back to our immune-complexes detection, we wanted to see whether there was any correlation between the level of immunoglobulin in the serum and the immunoglobulin in the circulating immune complexes in the same patients. Interestingly enough, for each one of the immunoglobulins we found absolutely no correlation (Fig. 6). This finding suggested that in the immunoglobulins inside the immune complexes, there might be a selective recognition of antigen. When we turned again to the patients with Crohn's disease exclusively, we found that the immunoglobulin levels in their circulating immune complexes were higher than normal, particularly the levels of IgG and IgA (Fig. 5).

Searching for a Marker. Now, going back to the entire group of patients, once we isolated the immune complexes, we subjected them to electrophoresis and tried to separate the antibody component of the immune complex from the antigen; we were looking for an antigen that would be more specific to the disease. I must say that the problem is quite complicated. I don't think one can draw any firm conclusions from what we have seen so far. Fig. 7 shows an SDS-Page gel with a hazy new line above the IgG in the colorectal cancer samples. In two of three patients with ulcerative colitis, there is a second band on the electrophoresis gel immediately past the IgM. We are trying to identify these bands and see what they mean, if anything, or whether we are working with "kitchen artifacts."

Then we, of course, also studied the tissues (Fig. 8). For example, we took the diseased tissues from one Crohn's disease patient and the apparently normal margin of resection, passed it through a sucrose gradient, and tried to see if we had anything that could represent a specific antigen. In the diseased tissue we see a band that we don't see in the normal tissue. The problem is that in one sample, we see some lines, and in the next one we see nothing at all.

This is ongoing work and we are looking for something that seems to be quite elusive. Nevertheless, we believe that this search for a marker that would be better than the carcinoembryonic antigen we are now using is promising.

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Prostate Cancer: Clinical Trials of Gonadotrophin-Releasing Hormone Analogs as an Alternative to Orchiectomy

Vincent Hollander, M.D., Ph.D.

Huggins' studies in the 1940s showed that prostatic tissue used male hormone as a growth substance, and that prostatic cancer could be put into remission by orchiectomy or estrogen treatment. Huggins' early studies involved measurement of the prostatic-secretion volumes from orchiectomized dogs. The prostate has little secretion after castration but administration of testosterone to such animals immediately increased the secretory volume and the size of the prostate, which had atrophied after removal of the testes. Huggins then went on to do orchiectomy on patients and soon demonstrated that most such patients would experience a remission, at times spectacular but usually lasting no longer than two years. Similar results are obtainable with administration of diethylstilbesterol (DES). The dose of DES must be carefully adjusted to prevent increased cardiovascular disease in patients who are in remission from cancer. The main problem, however, is the relapse which occurs after castration-induced remission.

The benefit derived from androgen control is often impressive and rapid. Evidently, most of the benefit can be ascribed to the loss or inhibition of androgen.

The relapse cannot so easily be explained. Animal experiments show that before rat prostatic tumors are treated by orchiectomy, they contain cells that can grow at androgen levels equivalent to those in castrated animals. It has been assumed that the regrowth of tumor is not an adaptation to a low-androgen environment but rather the spontaneous emergence of cells that occur as a result of random mutation and that can grow in the absence of androgen. Careful inspection of the data for this belief shows that the experiments actually demonstrate that experimental tumors which have regressed after orchiectomy regrow in the castrated animal and can be transplanted to either castrated or female animals. This of course does not prove the common belief that the cells are growing in the absence of androgen.

In order to study the mechanism of relapse, it would be helpful to have an agent that reversibly controls the production of androgen and readily reduces circulating androgen levels to the castrate level. Such an agent is available today in agonist-analogs of gonatrotrophin-releasing hormone. Gonadotrophin-releasing hormone (GnRH) is made in the hypothalamus and enters the circulation of the pituitary by means of the hypophyseal portal circulation. GnRH stimulates pituitary cells to secrete follicle-stimulating hormone and luteinizing hormone (LH). When GnRH was discovered, there was great hope that it could be used in the solution of clinical fertility problems. It was then found that chronic administration of GnRH agonist-analogs behave in a quite different manner from that seen after acute administration. Chronic administration results in down-regulation of the pituitary response, as well as a direct effect on gonads, so that the response to gonadotrophin is inhibited. Therefore, there is a diminution in testosterone secretion by means of two mechanisms. There is actual reduc-

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tion in LH secretion, and reduced response by the testis to LH stimulation to secrete testosterone. The down-regulation occurs when GnRH is given by infusion or by injection at some constant rate, such as by daily subcutaneous administration. However, pulsatile administration of GnRH agents intravenously avoids the down-regulation, and GnRH is once again useful in treating fertility as well as in reducing testosterone secretion.

One might anticipate, then, the sequence of events on initial injection of a GnRH analog for the first few days and the response that would be attained once chronic administration is in progress. At the first few injections of the analog, one sees the expected rise in plasma LH and subsequent rise in plasma testosterone. Occasionally, therefore, one might predict an adverse effect of analog treatment, since some prostatic cancers might be stimulated to grow by the transient flare in androgen concentration.

Buserelin Treatment. Many agonist-analogs are available; they were made because the natural hormone is unstable in circulating blood, and analogs can readily be created which are not only more stable but which also have higher binding constants to pituitary cells. We at The Mount Sinai Medical Center have been using buserelin for the treatment of advanced prostatic cancer. We have selected patients who have prostatic cancer, Stage C or D, and who have had no previous chemotherapy or hormone therapy. After carefully explaining the treatment to the patient, and obtaining informed consent, treatment is started by teaching the patient to administer buserelin subcutaneously. The hormone can be given by the subcutaneous route or intranasally. Although the substance is well absorbed by the latter route, we have preferred to give the material subcutaneously until the initial clinical trials were completed. There has been no difficulty in teaching patients to give themselves regular injections of buserelin. For one week, 500 mcg is administered every 8 hours. Thereafter, 200 mcg is given once daily, and this treatment continues until relapse.

We can report on the results of treating 12 patients, ten of whom are evaluable. All ten of the patients benefited in some manner. Seven of the patients showed regression of local prostatic tumor. Two patients showed improvement in bone scan, and the other patients were stable, with the exception of two, who showed improvement or stability in the bone scan until relapse. Two of the patients showed resolution of lung metastases. In one of these patients, the improvement was radiologically complete and clinically dramatic. This patient, over 80 years of age, was incapacitated by hemoptysis which occurred more than 20 times a day. After one month of treatment, hemoptysis ceased, and the pulmonary metastases disappeared; he returned to full activity. We have seen improvement in hematologic disease in one patient with proven marrow involvement. Of six patients with severe bone pain, two became completely pain-free, and four showed significant but partial pain relief. Two patients have relapsed, one after nine months of treatment. This patient had severe marrow replacement with very low platelets, and died four months after relapse from sepsis. Another patient relapsed after six months of treatment, with bone and soft tissue progression, and died about three months after relapse. The two patients who relapsed showed complete relief of very severe bone pain, and one of these patients showed improvement in bone scan.

There is little doubt that buserelin is an effective agent; comparison with castration and DES as initial treatment is not possible. Further work is necessary to understand the mechanism by which all patients treated by hormonal modalities relapse. Prostatic cancer is a difficult disease to evaluate, and physicians are handicapped by any modality of treatment because of the low growth-fraction and the essential genetic instability that gives rise to cells resistant to most forms of treatment. Many forms of treatment are available, yet we have surprisingly little to offer patients once they have relapsed from endocrine-induced remission. Progestational agents, ketoconazole, cyproterone acetate, aminoglutethimide, hypophysectomy, adrenalectomy, and chemotherapy are all useful in treatment of the disease. However, we will not really improve the outlook of patients with this common neoplasm until we understand the biochemical mechanisms controlling the growth of these cancer cells and the mechanism by which they escape the different forms of hormonal control.

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Summary

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The trend in the past few years in the field of surgical oncology and in oncology in general has been toward multidisciplinary approaches to the treatment of malignant disease. For many years, surgery was the only treatment of cancer, and obviously it did not resolve many of the problems. When radiotherapy and chemotherapy came along, each was looked to as the definitive answer, but again, problems remained. We realized then that we had to all put our efforts together.

I think if we look back and analyze the progress, the cancers that we are managing the best nowadays are those in which we have indeed put efforts together: testicular cancer, ovarian cancer and in many cases uterine-cervical cancer, and the lymphomas. In breast cancer, particularly, the emphasis now is on the nature and biology of the disease: It is not the techniques of surgery that make a tremendous difference in the outlook for the patient, but working with the biology of the disease in the treatment that one is applying. In that respect, our institution has been and continues to be very active in leading research toward the best way of identifying patients for the different strata of treatments.

I think that one of the main points made by Dr. Glenn and by Dr. Holland is that once a cancer center is established, once an institution like ours includes all the aspects of this multidisciplinary approach, it is extremely important to have a relationship with the community in which there is a continuous interchange of information. For good progress to be made, the institution and the community must work hand in hand. The patient may move between the institution and the community—may first be seen in the community, be referred to the cancer center, participate in a study, return to the community; the patient may receive one part of the treatment in the cancer center and another in the community. But the entire process should be planned from the beginning; the community and cancer center should function together systematically as part of a single network.

That seems to be the way of the future. The places where the best results are achieved in treatment are those in which the approach is well-planned, from the very beginning of the patient's presentation, and then is fully carried out. By contrast, when a patient undergoes a certain surgery without any further workup and is found to have disease "X" and then is referred for further treatment elsewhere, and so on, all haphazardly, the best results are not obtained.

I think the emphasis in these papers has been on the fact that we are tending more and more toward combined treatment and at the same time, perhaps, less radical surgery. Dr. Sherry has discussed very important surgery that preserves the limb and the function and decreases mutilation. Dr. Aufses has commented upon the possibility of performing smaller operations on cancers of the rectum and yet by adjunctive treatment, preoperatively or postoperatively, achieving a better result than with the more extensive surgery by itself. I think this applies more and more. Dr. Biller's paper, in which he has outlined many radical surgeries that try to conserve function, is extremely important. These head-and-neck surgical patients, until just a few years ago, were frequently converted into "freaks" by surgery, because there was a tremendous mutilation. Now we have far more adequate rehabilitative and reconstructive techniques that considerably improve results.

In the investigative aspect of our work, we have shown only part of what we are actually doing; our interests are mainly represented in the search for new ways of treating different cancers more innovatively and of detecting the disease earlier and thus improving therapeutic efficacy.

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General Articles

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Experimental Colitis and Colonic Cancer in the Rat

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Abstract

Experimental colitis has been produced in rats by means of topical acetic acid. Subsequent treatment with the colonic carcinogen 1,2-dimethylhydrazine resulted in a greater-than-expected incidence of colonic cancer in the colitic rats, with the neoplasms situated especially in the colonic mucosa which had been exposed to acetic acid. We conclude that experimental colitis sensitizes the rat colon to the carcinogenic action of an exogenous colonic carcinogen. The model has implications for the genesis of colitis-associated colonic cancer in humans and will also provide a useful technique for screening suspected environmental colonic carcinogens.

Many reports have indicated that the clinical course of ulcerative colitis is complicated by the development of carcinoma of the colon (1–3). We have attempted to reproduce these clinical circumstances by studying the effect of experimental colitis in rats on the development of colonic cancer in response to an exogenous colonic carcinogen (1,2-dimethylhydrazine).

Methods

All studies were performed with male Wistar rats, weighing 621 ± 93 gm. Colitis was induced in the rats by two experimental techniques. MacPherson and Pfeiffer (4) had recommended injecting 0.5 ml of 10% acetic acid into the lower colon through a 1.2-cm length of PE 240 plastic tubing, the end of which was sealed. The tubing had four rows of perforations around the circumference, with 0.5 mm between perforations. Instillations of acetic acid were followed by two instillations of 150 mmol/L sodium chloride. We modified this technique to use a catheter 12.5 cm long, perforated in the same manner. The strength of the acetic acid was also varied from 10% to 25%. Since this method was found to be unsatisfactory, in a pilot study, we changed to the technique described by Mann et al. (5), who injected 1.5 ml of 10% acetic acid through 3 cm of unsealed, unperforated PE 240 tubing, followed by two washes of 1.5 ml of 150 mmol/L sodium chloride. Both methods were assessed by killing the rats 2 weeks after induction of colitis. The colons were removed intact and then sectioned at 1.5, 6, 12, and 18 cm from the anal margin. The severity of the colitis was graded according to the criteria described by MacPherson and Pfeiffer (4).

In the studies of carcinogenesis, three groups of 14 rats each were used. Group A had colitis as the result of intrarectal instillation of acetic acid, and each of the rats received subcutaneous injections of the control vehicle for the carcinogen (EDTA). Group B received control enemas of saline and subcutaneous injections of 1,2-dimethylhydrazine (DMH). Group C had colitis and also received injections of DMH. The rats were weighed weekly.

DMH (Sigma London Chemical Co., Poole, Dorset, England) was prepared in fresh solution in 1.5 mmol/L EDTA (British Drug Houses, Poole, Dorset, England) and adjusted to pH 6.5 with 0.1 mol/L sodium hydroxide. Control animals received subcutaneous injections of the EDTA alone, and DMH was injected subcutaneously in a dose of 20 mg/kg body weight at the time of induction of colitis and weekly thereafter, until the animals were killed 20 weeks later.

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After death, the colon was removed intact and mucosal lesions were assessed with a dissecting microscope. Numbers of neoplastic lesions were recorded. Sections for histologic examination were fixed with formol saline and stained with hematoxylin-eosin. Complete transverse sections of the colon were taken at 1.5 cm from the anal margin. In addition, all focal mucosal abnormalities and macroscopically obvious tumors were recorded in terms of distance from the anal margin and examined microscopically. The peritoneal cavity and liver were examined for metastatic lesions. All histologic examinations were carried out without knowledge of the experimental circumstances.

Results

Colitis Models. The perforated, sealed 1.2-cm tube produced colitic lesions consistently only in the distal 1.5 cm of the colon. Increasing the length of the tube, or the strength of acetic acid, produced only patchy inconstant lesions in the distal 12 cm of the colon. On the other hand, use of the 3-cm unsealed tube (5) resulted in consistent lesions in the distal 6 cm of the colon. The latter method was therefore used for the study of carcinogenesis.

Carcinogenesis Studies. Ten rats had to be killed before the end of the study. Findings at autopsy are shown in the Table. The remaining animals showed the following:

Group A (Colitis Only). Four animals showed colonic mucosal irregularities, comprising lymphoid patches in three animals and a benign ulcer 3.5 cm from the anal margin in the other rat.

Group B (DMH only). Eleven of the rats had 19 colonic adenocarcinomas. The other two animals had no colonic lesions. None of the carcinomas had metastasized.

Group C (Colitis plus DMH). Seven of the rats died from severe colitis and megacolon (Table). The six surviving rats had 25 adenocarcinomas without metastases. One of the rats also had a pancreatic carcinoma with metastases to the liver.

The number of tumors per rat was significantly greater in group C than in group B ($p < 0.01$) (Fig. 1), and the group C cancers were significantly closer to the anus ($p < 0.01$) (Fig. 2). All adenocarcinomas were moderately well differentiated, and their extent was similar in groups B and C. Thus, tumors in one rat of group B and three of group C were confined to the mucosa; 14 of group B and 18 of group C were submucosal; three of group B and two of group C had extended into the muscularis externa; and one of group B and two of group C had extended through the muscularis externa.

The histologic appearances of the macroscopically normal colon of groups A and C were not significantly different in terms of chronic inflammation and infiltration with inflammatory cells.

Discussion

We found that the model for producing experimental colitis in rats described by MacPherson and Pfeiffer (4) was not satisfactory for producing consistent, reproducible colitis, whereas the technique described by Mann et al. (5) not only was simpler, but did give consistent results. The severity of the colitis resulting from the intracolonic instillation of acetic acid was greatly increased by the administration of DMH, so that half of the experimental group with the latter combination (colitis plus DMH) died of severe colitis with toxic megacolon. The potentiating interaction between acetic acid and DMH is presumably attributable to the toxic effects exerted by DMH on the colonic mucosa during the first 72 hours after administration of the DMH (6), although the DMH, by itself, does not cause significant ill health of the animals. It seems possible that our experimental combination of chemically induced colitis, together with an agent that interferes with normal replication of the colonic mucosa (such as DMH), may provide an inter-

TABLE
Autopsy Findings in Rats Killed Before End of Study

Week of study	Number of rats	Experimental group	Autopsy findings
1	3	C	Severe colitis; colonic dilatation
2	4	C	Severe colitis; colonic dilatation
4	1	A	Colonic stricture 8 cm from anus
10	1	C	Ascites; fatty liver; no cancer
16	1	B	Jejunal adenocarcinoma; no colonic cancer

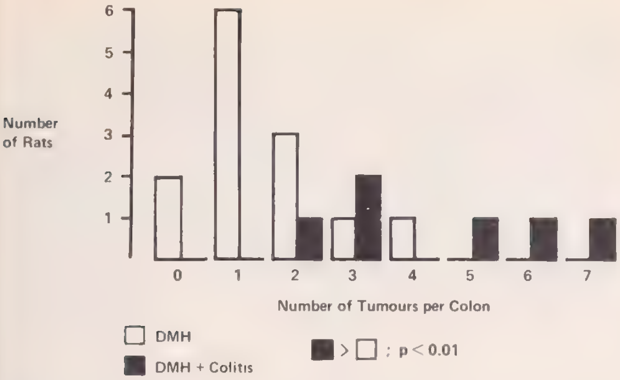

Fig. 1. Number of colonic adenocarcinomas per rat. Open columns indicate rats treated with DMH only; closed columns denote rats with colitis located with DMH. Significance assessed by Wilcoxon test.

esting and useful model for the study of toxic megacolon in humans.

The principal aim of the study was to determine whether the presence of colitis sensitizes the colon to the carcinogenic effect of an exogenous carcinogen, just as experimental pancreatitis sensitizes the pancreas to an exogenous pancreatic carcinogen (7).

Our results show that experimental colitis does increase the incidence of colonic cancer in response to the carcinogen (DMH) and also tends to determine the location of the cancers in the distal colon, which has been affected by the colitis. That inflammation and repair do promote colonic carcinogenesis and its localization is also shown by the predilection for azoxymethane-induced carcinomas in rats to occur at the line of suture after colonic transection (8, 9) or at the site of nonspecific colonic injury (10).

The study has implications for human colonic disease. There has been considerable controversy about the incidence of malignancy in preexistent ulcerative colitis in different parts of the world (1–3). It seems possible that the different incidence rates are attributable mainly to the difference in prevalence and duration of exposure of colitic patients to environmental colonic carcinogens. If the latter hypothesis is correct, search for and identification of such environmental colonic carcinogens may be made technically feasible by using the rat with experimental colitis as screening model.

Acknowledgments

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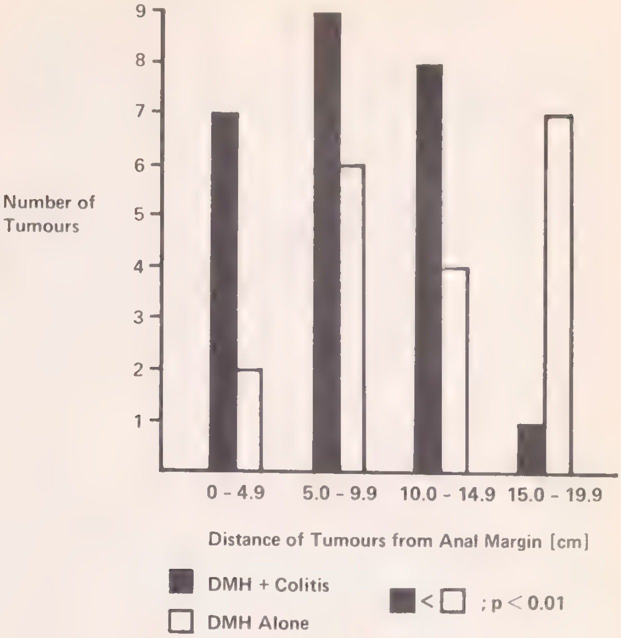

Fig. 2. Distance of colonic carcinomas from anal margin (cm). Significance of symbols as in Figure 1.

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Cystic Islet Cell Tumor: Diagnosis and Surgical Management

DAVID A. LOITERMAN, M.D., IRA S. SCHWARTZ, M.D., AND ARTHUR H. AUFSES, JR., M.D.

Abstract

Although pseudocysts comprise three fourths of cystic lesions of the pancreas, a generally unappreciated fact is that more than 10% of pancreatic cysts are neoplastic. The presentation, diagnosis, management, and 1-year follow-up of a patient with an islet cell tumor presenting as a pseudocyst are discussed. A computerized search of the world literature over a 30-year period yielded only six previously recorded cases of cystic endocrine pancreatic tumor. Ultrastructural as well as immunocytochemical analyses were utilized to confirm the endocrine nature of this neoplasm. Finally, the differential diagnosis and management of this rare entity are addressed.

Islet cell tumors of the pancreas usually manifest by either functional hormonal activity or metastasis. Presentation of these endocrine tumors as cystic lesions is extremely rare. A computer-assisted title search of the world literature over the last 30 years produced only six cases of cystic islet cell tumor (1–5). Because of the infrequency of this tumor, as well as the lack of diagnostic, management, and follow-up data, the following case report is presented.

Case Report

A 60-year-old white man was admitted to The Mount Sinai Hospital in New York with a 9-month history of right-upper-quadrant colicky pain associated with fatty food intake. He denied having fever, chills, jaundice, hepatitis, alcoholism, trauma, diabetes, or watery diarrhea. Investigation of this problem prior to admission included sonography and contrast studies of the gastrointestinal tract and hepato/biliary-pancreatic tree. Abdominal sonography documented the presence of gallstones as well as a 5-cm midpancreatic cystic structure (Fig. 1). The upper gastrointestinal contrast study demonstrated a hiatus hernia, thickened gastric folds, and a normal duodenal sweep. Endoscopic retrograde cholangiopancreatography revealed a normal common bile duct and ampulla, but nonfilling of the pancreatic duct. On the day prior to admission, the patient developed chills, colicky midepigastric pain, and bloating.

At the time of admission, the physical examination was remarkable only for an oral temperature of 100.5°F and a distended abdomen with palpation-induced midepigastric tenderness. The white blood cell count was 12,000/mm^3 with 10% immature forms. Significant serum chemical analysis showed a glucose concentration of 77 mg/dl and an amylase level of 510 units (normal 40–240 units). The calcium level was normal. A presumptive diagnosis of biliary tract disease, recurrent pancreatitis, and pseudocyst was made, and the patient was taken to the operating room. At laparotomy, the head of the pancreas was indurated, but edema, fibrosis, and fat necrosis, indicative of chronic pancreatitis, were not seen. A cystic lesion, approximately 5 cm in diameter, occupied the body of the pancreas. The gallbladder contained multiple stones.

Cholecystectomy, distal pancreatectomy, and splenectomy were performed. An intraoperative cholangiogram demonstrated a normal bile duct. A pancreatogram, produced by inserting a cath-

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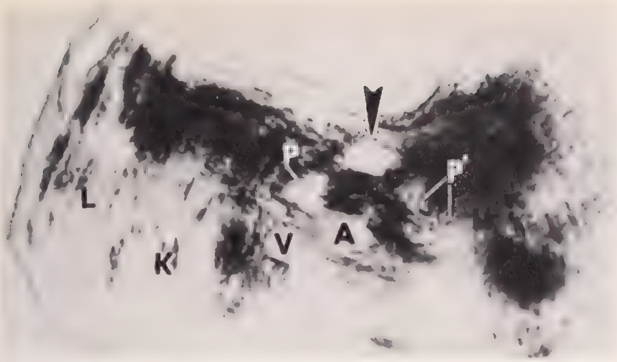

Fig. 1. Abdominal sonogram. Transverse scan, 12 cm above umbilicus. P, head of pancreas; P′, tail of pancreas; L, liver; K, right kidney; V, inferior vena cava; A, aorta. Cystic lesion is located in body of pancreas (arrowhead).

eter through the cut end of the duct at the line of resection, demonstrated free flow of contrast into the duodenum with no ductal abnormality. The open end of the pancreas was then implanted into a Roux-en-Y jejunal loop.

The early postoperative course was stormy. The patient developed clinical and X-ray evidence of peripancreatic abscess formation, which required drainage 3 weeks after the initial surgery. Profuse drainage continued and was eventually proven to come from a leak at the site of implantation of the pancreas into the Roux loop. Although all of the pancreas to the right of the mesenteric vein was spared, insulin-dependent diabetes occurred in the early postoperative period.

The patient was discharged from hospital 6 weeks after his initial operation with a drainage tube in situ in the left upper quadrant. Six weeks after discharge, drainage ceased and the tube was removed.

One year after surgery, the patient's wounds are healed; he is asymptomatic and has returned to work. However, daily insulin is still required for control of diabetes.

Pathological Findings

The segment of resected pancreas was 13 cm long (Fig. 2). A cyst near the proximal resection margin, measuring 4.0 cm in greatest diameter, contained a small amount of brown, soft granular material. It had a somewhat shaggy brownish-tan lining without papillation, bordered by a narrow band of tan tissue, averaging 0.1 cm in thickness. External to this was a whitish-gray fibrous capsule. A small amount of normal pancreatic parenchyma constituted the resection margin. The parenchyma distal to the cyst appeared moderately fibrotic; the main pancreatic duct could be traced retrograde from the cyst margin and was moderately dilated. Multiple tributaries of the major duct showed cystic dilatation, some containing calculi.

Histologic examination of multiple sections taken through the perimeter of the cyst revealed a neoplastic proliferation of uniform epithelial cells comprising the narrow lining grossly observed. These cells were arranged in a ribbonlike trabecular pattern with a delicate intervening vascular stroma, characteristic of islet cell tumors. The cells exhibited round or oval regular nuclei and finely granular pale cytoplasm. There was no mitotic activity. The tumor was separated

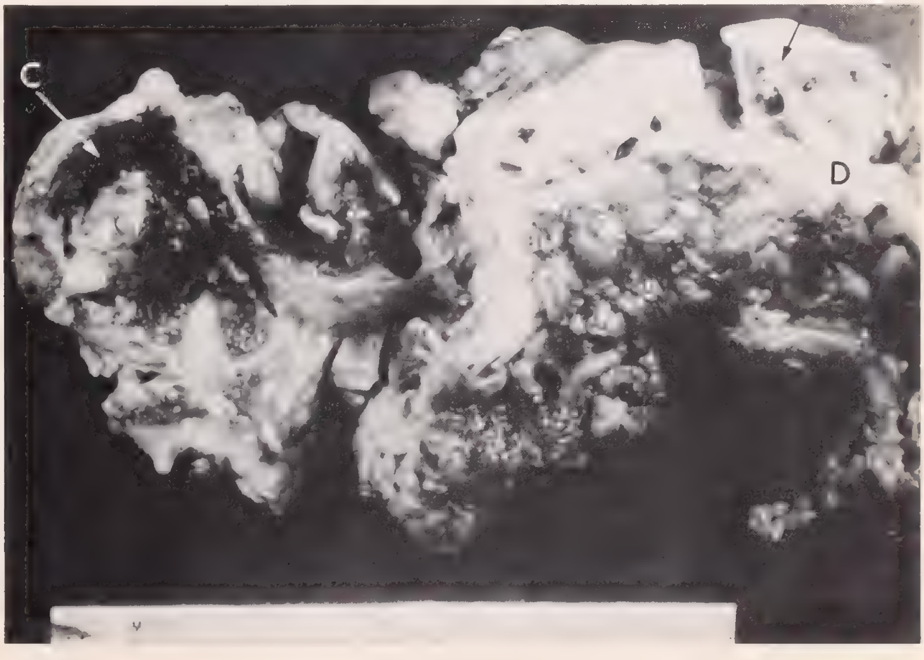

Fig. 2. Gross appearance of resected specimen showing cystic tumor (C) near proximal margin, dilated pancreatic duct (D), and calculus in duct tributary (arrow).

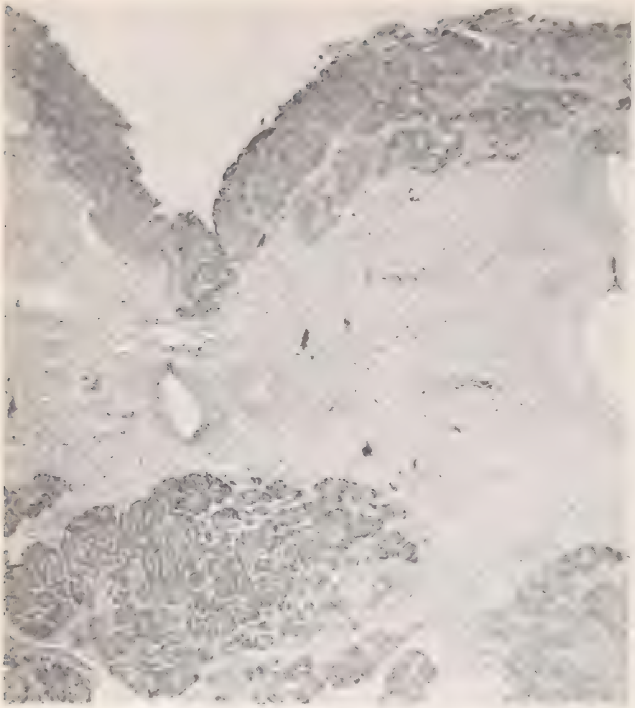

Fig. 3. Photomicrograph of cystic islet cell tumor at low magnification showing tumor lining cystic cavity and separated from adjacent pancreatic parenchyma by fibrous tissue.

from adjacent pancreatic parenchyma by a wide margin of fibrous tissue showing mild chronic inflammatory cell infiltration (Fig. 3). All 13 peripancreatic lymph nodes identified in the specimen were free of tumor. Argyrophil granules (Grimelius stain) were demonstrable in the cytoplasm of the tumor cells and tended to be concentrated toward one pole of the cells, adjacent to stromal capillaries (Fig. 4).

Ultrastructural study, performed on glutaraldehyde-fixed tissue embedded in Epon and stained by osmic acid and lead citrate, revealed plentiful cytoplasmic membrane-bound neurosecretory-type granules measuring up to 100 nm, corresponding to the argyrophilic granules seen by light microscopy (Fig. 5).

In an attempt to demonstrate intracellular hormonal products, the peroxidase-immunoperoxidase method was used with appropriate antisera and positive controls to detect the presence of the following ten substances in the tumor: insulin, glucagon, gastrin, serotonin, ACTH, somatostatin, vasoactive intestinal polypeptide, human chorionic gonadotropin, follicle-stimulating hormone, and carcinoembryonic antigen (courtesy of Dr. Cecilia Fenoglio, Department of Surgical Pathology, Columbia University College of Physicians and Surgeons). Immunostaining was negative for all ten substances. This correlated with the absence of any clinical endocrine disturbance.

Discussion

Although pseudocysts account for 73% (6) of cystic pancreatic masses, a fact not generally appreciated is that 13% represent primary cystic neoplasms (7). An almost equal percentage, 11%, are retention cysts (7), whereas only 3% are of congenital origin (6).

Cystadenomas and cystadenocarcinomas are of ductal epithelial origin and comprise more than 98% of pancreatic cystic neoplasms. The other less frequent neoplastic cysts of the pancreas are leiomyosarcomas and rhabdomyosarcomas that

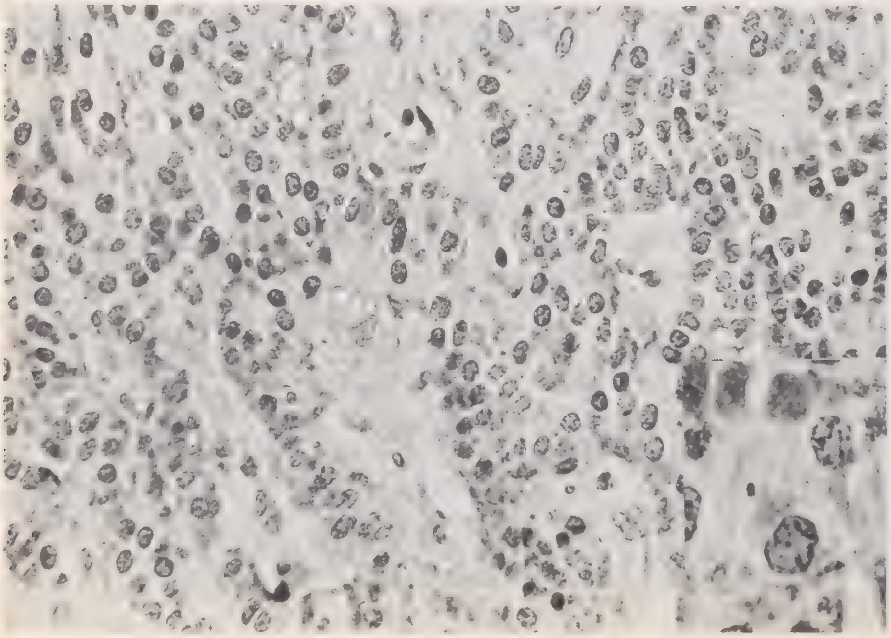

Fig. 4. Uniform cells of islet cell tumor in trabecular arrangement. Argyrophil granules are demonstrable toward one pole in many cells (inset) by Grimelius stain.

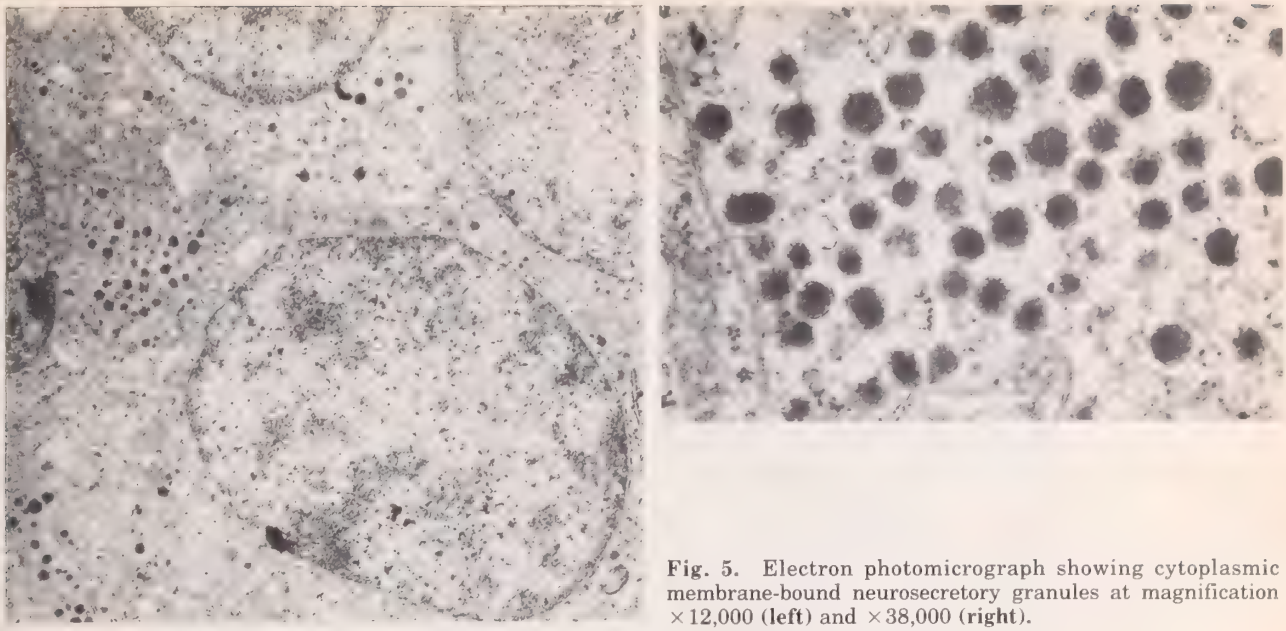

Fig. 5. Electron photomicrograph showing cytoplasmic membrane-bound neurosecretory granules at magnification ×12,000 (**left**) and ×38,000 (**right**).

have undergone cystic degeneration. Islet cell tumors with a cystic architecture are exceedingly rare.

Only six cases have been reported in the last 30 years (1–5). Four of the patients were men. The age range was 34 to 75 years; three of the six were over 60. These patients presented with abdominal pain, an epigastric mass, or constitutional symptoms such as malaise or weight loss. Excessive ethanol intake was not a prominent feature in the medical history of these patients, although several had a history of pancreatitis. The most common preoperative diagnosis was pseudocyst. In all cases, treatment included surgical resection. Because of the small number of cases reported, it is at present unclear whether actuarial survival for patients with this variant is different from that of solid islet cell tumors of similar histology, which are usually slow-growing (8). Since cystic islet cell tumor is rare, additional cases will have to be accumulated before the natural history can be determined.

In the case reported here, the patient was not an alcoholic and had documented cholelithiasis with recent onset of acute pancreatitis. At laparotomy, the head of the pancreas was grossly normal. Because pseudocyst formation is not commonly associated with biliary pancreatitis and there was no other strong evidence supporting the diagnosis of chronic pancreatitis, resection, rather than cystoenterostomy or cystogastrostomy, the usual treatment of pancreatic pseudocyst, was deemed appropriate (9).

Unlike solid pancreatic cancer, cystic neoplasms may present as pseudocysts, and the surgeon must decide intraoperatively how to manage any given cystic lesion. Since 13% of all pancreatic cysts are neoplastic, it seems that resection with adequate margin would constitute appropriate management for any cystic lesion of the pancreas not clearly a pseudocyst.

Acknowledgments

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Doses to Organs at Risk from Mantle Field Radiation Therapy Using 10 MV X-Rays

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Abstract

Estimates of the doses to organs at risk from mantle field radiation therapy using 10 MV x-rays are presented. Doses were estimated using TLDs in an anthropomorphic phantom. The doses to the gonads and fetus with and without a 1 mm lead equivalent shielding apron were measured. The doses to the fetus at early, mid, and late pregnancy without the shielding apron were estimated to be 63, 88, and 220 rad, respectively, when a total dose of 4,400 rad was delivered to the midline of the central axis. The doses to the ovary and testes were estimated to be 37 and 25 rad, respectively. There was no significant reduction in dose by using the shielding apron. The dose to the lens of the eye was estimated to be 360 rad, or 8.2% of the total dose. The dose was reduced to 160 rad, a 56% reduction, by utilizing lead eye shields.

Introduction

Advances in the overall treatment of Hodgkin's disease have led to increased life expectancy for these patients. Since some of these advances are directly due to radiation therapy, it is clinically important to evaluate the magnitude of secondary radiation to the organs potentially at risk from mantle field radiation therapy. The mantle field (1, 2) covers the lymph nodes of the neck, axillae, mediastinum, and hilar regions. Cerrobend blocks shield the lungs, humeral heads, larynx, and cervical spine (PA only). Generally, 180 to 200 rad is delivered to the midplane per fraction, 5 days per week, with a total dose of 4,400 rad at midline of the central axis.

Secondary doses to the organs at risk from extended field radiotherapy using various energy photons have been previously reported (2–7). In our review of the literature, we have found no estimate of the dose to the lens of the eye from mantle field therapy using 10 MV x-rays. Since the effects of radiation on the eye and the possibility of cataract development have been known for a long time (8, 9), it is the aim of this study to present dose estimates to the lens of the eye with and without a shielding device. In addition, the diagnosis of Hodgkin's disease during pregnancy has occurred (10), and most patients receiving radiation therapy are of child-bearing age (11, 12). Therefore, the secondary doses to the fetus at early, mid, and late pregnancy and to the male and female gonads were also estimated. These dose values are compared with the published data using different modalities. Because a study by Nüsslin and Hassenstein reported a reduction in dose of one-third by using a 1 mm lead shield (13), we estimated the doses to the gonads and fetus with and without a 1-mm lead equivalent shielding device.

Materials and Methods

Experimental dosimetry utilized an Alderson Rando phantom, human equivalent, composed of multiple horizontal sections. Thermoluminescent

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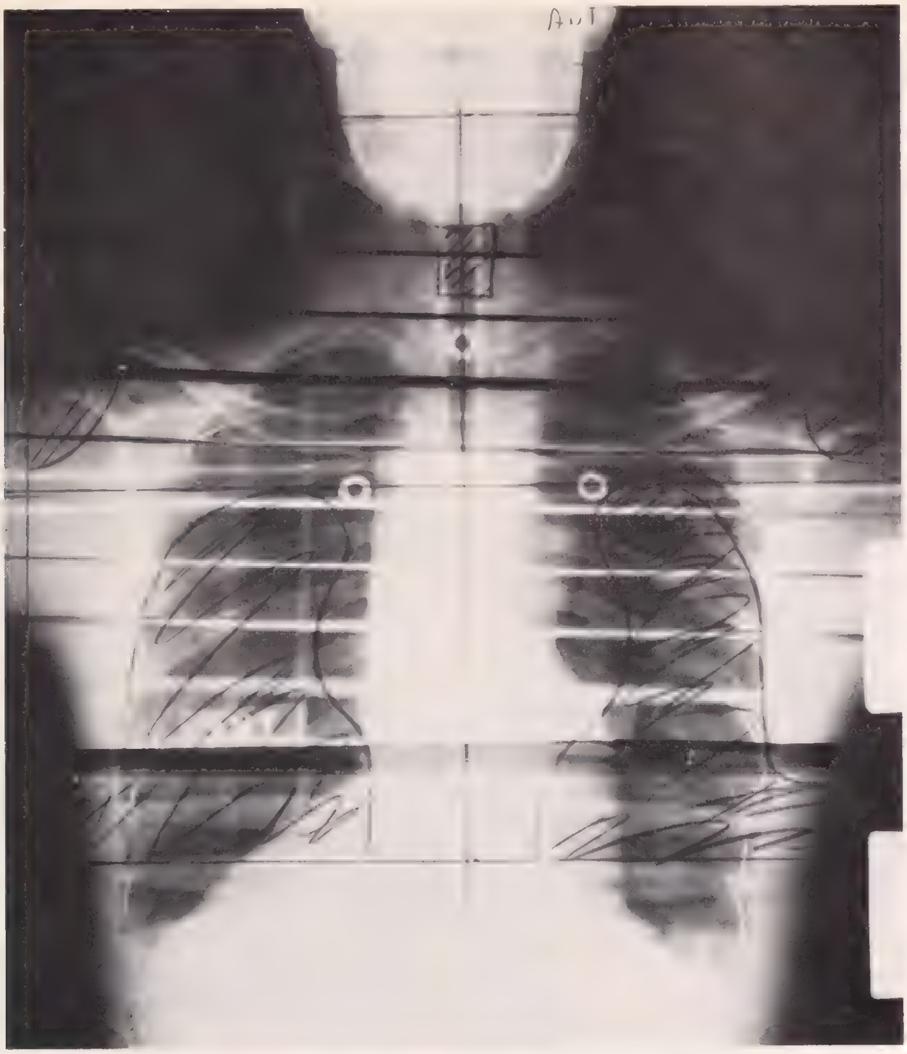

Fig. 1. Radiograph showing borders of mantle field.

dosimeters (Li F TLD-100 chips, Harshaw Chemical Company, Solon, Ohio) measuring 3.18 × 3.18 × 0.38 mm were placed in capsules which were then settled in the multiple abdominal slices which are 7.5 cm (slice 21), 15 cm (slice 24), 20 cm (slice 26), 30 cm (slice 30), and 38 cm (slice 33) from the inferior limit of the mantle field. The points of measurement for early, mid, and late pregnancy correspond to the L5, L2 to L3, and T12 to L1 levels of the vertebral column, respectively. The TLD annealing process recommended by the manufacturer (1 hr at 400° C followed by

TABLE 1

Contribution of Secondary Radiation Dose to Lens of Eye without Shielding during Mantle Field Treatment Using 10 MV X-Rays

	AP contribution	PA contribution	Total secondary dose
Dose (rad)	280	80	360
Percent of prescribed dose	6.4	1.8	8.2

(4,400 rad prescribed to midline of central axis)

TABLE 2

Effect of Lead Shielding on Dose to Lens of Eye during Mantle Field Treatment Using 10 MV X-Rays

	Without eye shield	With 1 mm lead apron over face	With lead shield over eyes
Dose (rad)	360	170	160
Percent of prescribed dose	8.2	3.8	3.6
Percent reduction	—	53	56

Shielding in place only during AP irradiation.

TABLE 3

Doses to Organs at Risk from Typical Mantle Field Treatment Using 10 MV X-Rays

Organ at Risk	Phantom slice number	Distance from inferior border of field (cm)	Dose (rad)	Percent of prescribed dose (4,400 rad)
	26*	20	63	1.4
Fetus	24†	15	88	2.0
	21††	7.5	220	5.0
Ovary	30	30	37	0.8
Testis	33	38	25	0.6

* Early pregnancy †mid pregnancy ††late pregnancy

2 hrs at 100° C) before each irradiation was followed.

For the measurement at the lenses of the eyes, 2 TLDs were placed on the top of the eyes. A 0.6 cc Baldwin-Farmer ionization chamber (model 2505/3) connected to a Baldwin-Farmer dosimeter (model 2502/3) was also used during the AP irradiation for confirmation. The effects of two different shields on the secondary dose were examined. Lead eye shields (model ES-801, Atomic Development Corp., Plainview, New York), which are commonly used in superficial x-ray therapy, were placed over the eye lids. There is no need to place these shields under the eye lids. The dose to the lens of the eye was also estimated with a 1 mm lead equivalent shielding apron draped over the face.

Opposed anterior and posterior mantle fields were positioned on the phantom using the established routines for patients. A radiograph of the field is shown in Figure 1. A Clinac 18 with 10 MV x-rays (Varian Associates, Palo Alto, California) was used. The source-skin distance was 130 cm with the central axis 5 cm below the suprasternal notch and a field size of 26 × 26 for AP and PA fields on the surface. Cerrobend blocks, 7.5 cm thick (HVL = 1.7 cm), were arranged to shadow the lungs and humeral heads. On the PA field, the cervical spine was also shielded.

Results

The breakdown of the secondary radiation dose to the lens of the eye is indicated in Table 1. The relatively high percentage contribution during the AP irradiation might be due to the low quality of the secondary scattered photons from the head of the unit and various sources of electron contamination during the irradiation. The magnitude of dose reduction using the lead apron and the lead eye shields is shown in Table 2.

The scattered dose without the shielding apron to the ovary, testis, and fetus at early, mid, and late pregnancy are indicated in Table 3. The doses resulted primarily from scatter within the patient and partially from scatter off objects in the room such as the floor and walls, and leakage from the head and collimator system. There was only minimal dose reduction when the shielding apron was placed on the abdominal area (Table 4), although experiments to reduce the dose from head leakage

TABLE 4

Effect of 1 mm Lead Equivalent Shielding Apron on Doses to Organs at Risk from Typical Mantle Field Treatment Using 10 MV X-Rays

	Without shielding		With shielding		
Organ at risk	Dose (rad)	Percent of prescribed dose (= 4400 rad)	Dose (rad)	Percent of prescribed dose (= 4400 rad)	Percent reduction
	63*	1.4	59	1.3	6.3
Fetus	88†	2.0	84	1.9	4.5
	220††	5.0	190	4.3	14.0
Ovary	37	0.8	33	0.75	11.0
Testis	25	0.6	22	0.50	12.0

* Early pregnancy †mid pregnancy ††late pregnancy

TABLE 5

Reports of Secondary Dose from Mantle Field Treatment to Organs at Risk as Percentages of Central Axis Dose

Author	Radiation quality	Fetus	Ovary	Testis
Meurk et al. (1968)	Co-60	(NA)	1.6	(NA)
Kartha et al. (1978)	4 MV	2	(NA)	(NA)
Covington et al. (1969)	6 MV	0.19–0.4*	(NA)	(NA)
		0.9–1.4†	(NA)	(NA)
		3.7–7.1††	(NA)	(NA)
Sharma et al. (1981)	10 MV	2.2§	0.5	0.3
Present study	10 MV	1.4*	0.8	0.6
		2.6†		
		4.9††		

* Early pregnancy †mid pregnancy †† late pregnancy.

§ Estimated from distances from lower edge of treatment field.

by optimal collimator angulation (14) and additional 8 cm thick lead blocking (7) have been reported.

Comparison of the secondary dose from mantle field treatment to organs at risk as percentage of central axis dose reported using different modalities is indicated in Table 5. Our data show the average fetus dose is slightly higher than others (4, 7), but the dose to the ovary is slightly lower than Meurk et al (5) utilizing Co-60. The slight differences may be due to differences in the radiation quality and experimental set up.

Discussion

In contrast to the findings of Nüsslin and Hassenstein (13), no significant reduction in dose to the abdominal organs at risk due to the lead shielding apron was found. Therefore, we do not recommend the use of the lead shielding apron for protecting gonads and fetus in mantle field therapy.

The effect of radiation on the lens of the eye has been known for many years (8, 9). Our data show that the secondary dose to the lens of the eye during the typical mantle field treatment of Hodgkin's disease using 10 MV x-rays was 360 rad, which is close to the 387 rad reported by Barnes et al (6) using 4 MV x-rays. These doses are at the level of the lower limit for cataract development in humans, with a probability between 0 and 1 as suggested by Merriam et al (9). The dose was reduced to 160 rad (or a 56% reduction), which is also close to the 187 rad reported by Barnes et al (6), by utilizing a simple lead eye shield during the AP irradiation. We have found no mention of cataract formation in reports of complications and late effects of mantle field therapy (15–18). However, Merriam has shown that incidence of cataracts starts at doses as low as 200 rad (9). Therefore, we recommend the use of the eye shields during AP mantle field irradiation. The simple and noninvasive nature of the lead eye shields provides the benefit of a 56% reduction in dose to the lens of the eye at minimal patient discomfort and cost.

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Hepatocellular Carcinoma Presenting as Sphenoid Sinus Metastasis

JENNY S. WAXMAN, M.D., BURTON SEIFE, M.D., AND MARIAN WAXMAN, M.D.

Abstract

We describe a patient who had ophthalmoplegia caused by a sphenoid mass; biopsy of the lesion revealed metastatic hepatocellular carcinoma. Literature on metastatic tumors to the paranasal sinuses is briefly reviewed. Isolated metastasis from the liver to the paranasal sinus is thought to occur by hematogenous spread via the paravertebral venous plexus.

Malignant tumors presenting with symptoms due to distant metastasis result in most unusual clinical manifestations. We are reporting a remarkable case in which the patient had what appeared to be a primary neurologic-ophthalmic disorder; investigation revealed hepatocellular carcinoma, completely unsuspected clinically.

Case Report. A 47-year-old man, a native of Guyana, was admitted to the hospital because of the acute onset of pain in the right eye, and diplopia. His history included a high intake of alcohol and occupational exposure to solvents and dusts used in sugar refining. Examination revealed ophthalmoplegia involving the right sixth nerve, but no other abnormal findings. X-ray thin layer tomography revealed a mass in the mid posterior sphenoid sinus without bone erosion (Fig. 1).

Computed tomography of the head in the axial and coronal planes (Fig. 2) confirmed the presence of a sphenoid sinus mass but demonstrated no intracranial extension. A carotid angiogram was normal. Open biopsy of the sphenoid sinus mass was performed. The mass separated easily from the underlying bone with little or no bleeding.

Pathologic examination disclosed aggregates of malignant epithelial tumor within the edematous upper respiratory mucosa. Some of the tumor clusters invaded the mucosa; others occupied vascular spaces (Fig. 3). Findings of cellular cords and trabeculae, multiple sinusoidal channels (Fig. 4) and bile droplets, were all characteristic and diagnostic of metastatic hepatocellular carcinoma. Attempts at demonstrating alpha-1 fetoprotein (AFP) by immunoperoxidase method in the small amount of tissue available were unsuccessful.

Subsequent Course. Abdominal CT demonstrated multiple masses in the liver (Fig. 5). Celiac and hepatic artery angiography showed vascular blush and abnormal vessel patterns consistent with hepatocellular carcinoma (Fig. 6). Chest x-ray was normal. Serum level of AFP was found to be markedly elevated (117 ng/ml), and levels of the alkaline phosphatase, LDH, SGOT, and SGPT were also abnormally high. Percutaneous liver biopsy attempt was unsuccessful on two occasions. A repeat CT study of the head one month later showed total opacity of the sphenoid sinuses and some of the left ethmoid cells, and fluid in both maxillary sinuses.

The patient underwent radiation treatment (4,000 rads within 5-week period to the sphenoid area). Four months later his neurologic status deteriorated, and he had bilateral ophthalmoplegia.

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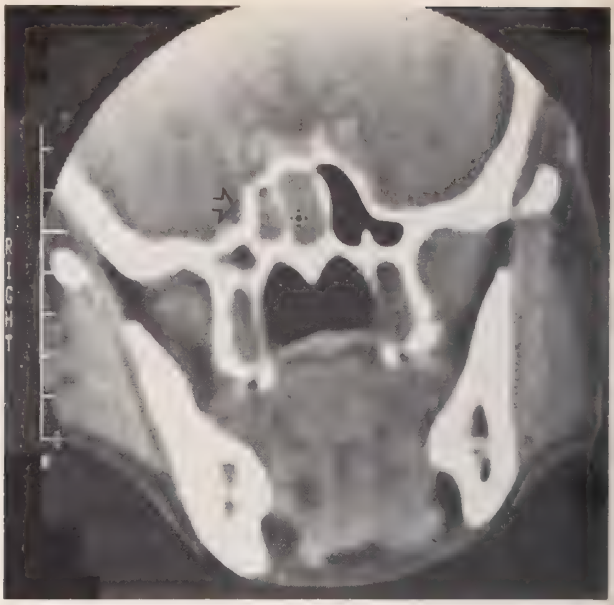

Fig. 1. Left Coronal tomographic cut at the level of anterior clinoids (arrows) shows sphenoid sinus with air to either side and above mass.

Fig. 2. Right CT in coronal plane two weeks after Fig. 1 was obtained; mass has enlarged to right (arrow).

His return to Guyana precluded further treatment and follow-up.

Discussion. Although metastatic tumors to the paranasal sinuses are uncommon, those involving the sphenoid sinus are distinctly rare. Bernstein et al (1) reviewed 72 cases of sinus metastases from the world literature and added their own 10 cases. The most common cancer metastatic to the sinuses was found to be carcinoma of the kidney, which exceeded by far all other sources (lung, breast, testis, gastrointestinal tract, and other); there was not a single case of metastatic hepatoma (1). Among these patients there were only six with metastasis to the sphenoid sinus (1). Three instances of metastatic carcinoma to the sphenoid sinus (two from the breast and one from

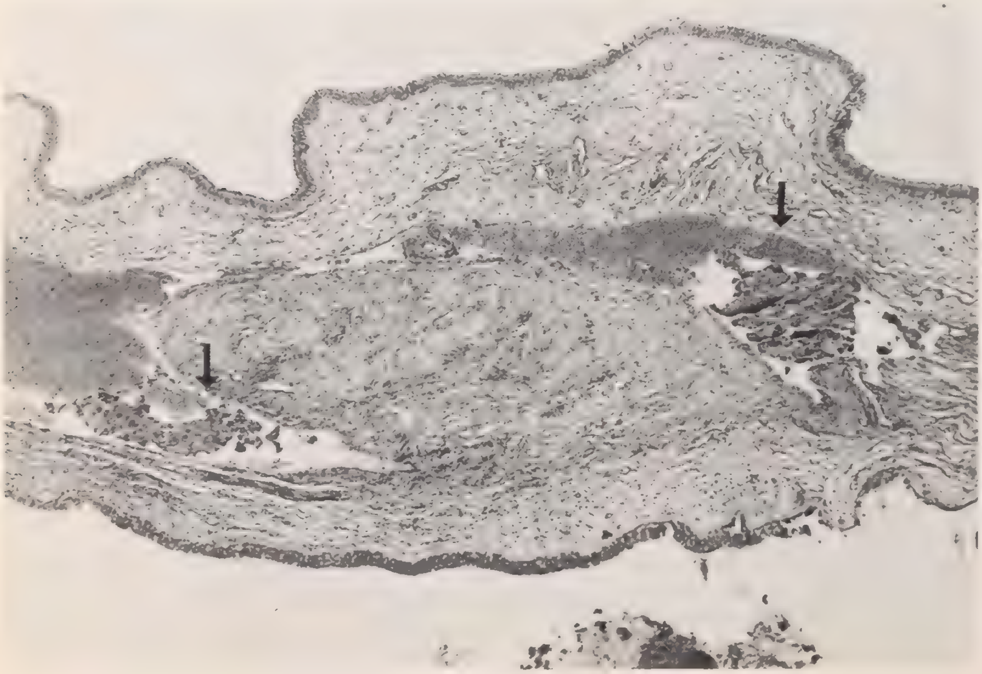

Fig. 3. Tumor emboli (arrows) seen in dilated vascular channels of respiratory mucosa (PAS, original magnification, ×100).

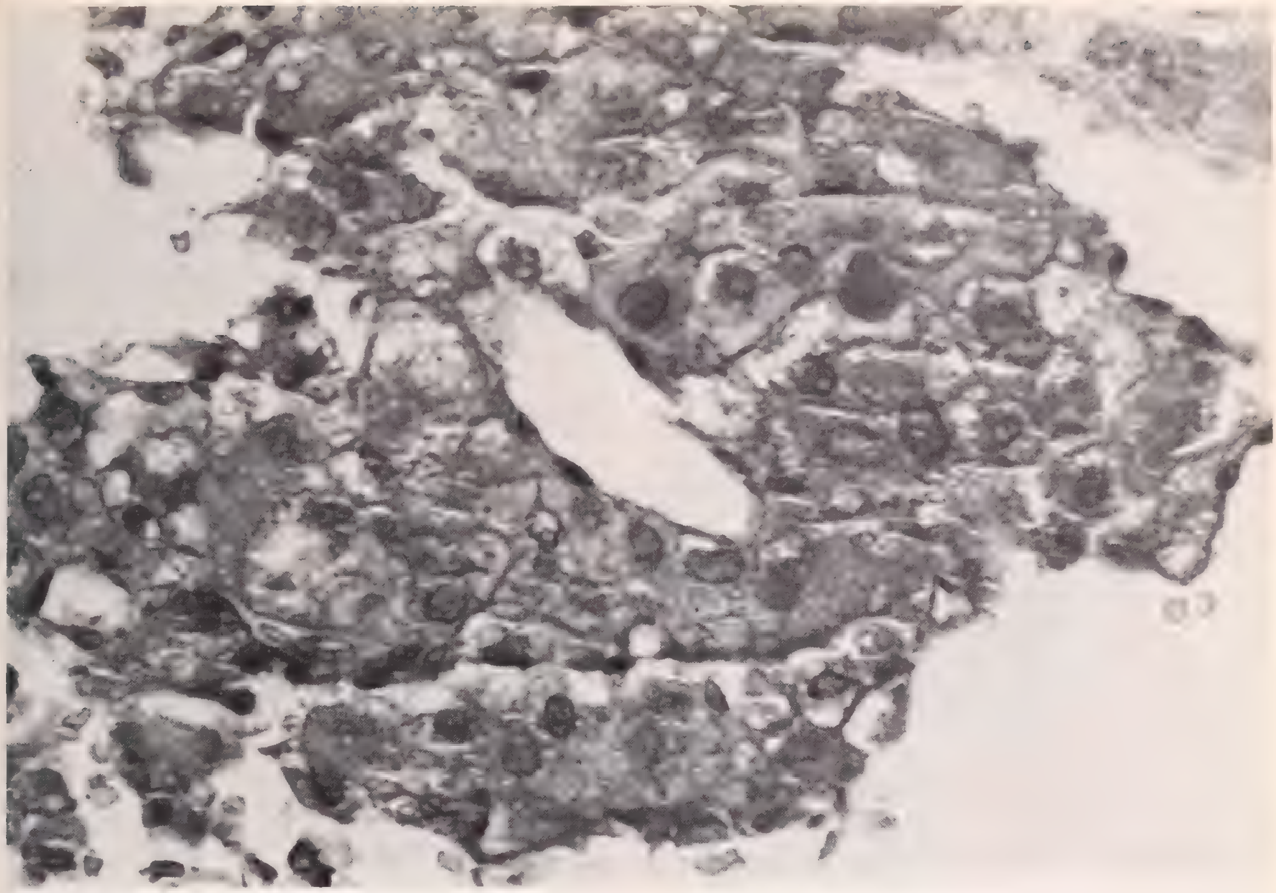

Fig. 4. Closeup of metastatic hepatocellular carcinoma showing characteristic cell morphology and central sinusoidal vessel (hematoxylin and eosin, ×400).

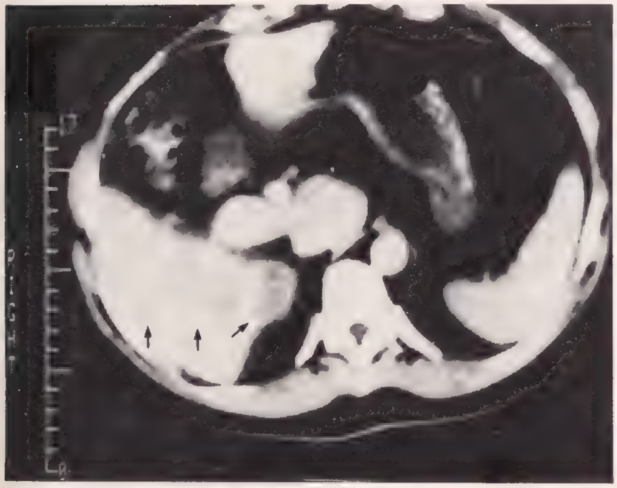

Fig. 5. **Left** Representative image from abdominal CT study reveals multiple areas of decreased attenuation (arrows).

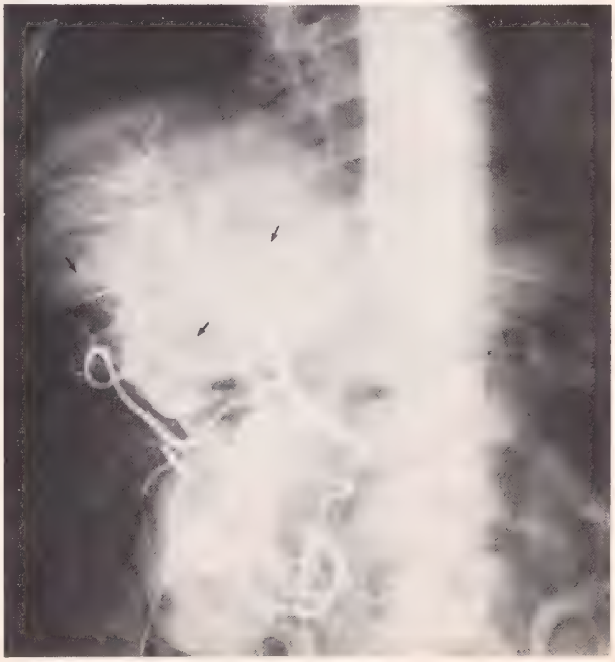

Fig. 6. **Right** Hepatic angiogram shows multiple areas of hypervascularity with abnormal vessels (arrows).

the stomach) were found among 40 patients with tumors metastatic to the oral cavity, pharynx, and paranasal sinuses, representing records at the M.D. Anderson Hospital and Tumor Institute over a 25-year period (2).

Barrs et al collected eight instances of metastatic tumor to the sphenoid sinus seen in Mayo Clinic during a 27-year period; in four of these patients the location of primary cancer was unknown at the time of presentation (3). A case similar to ours, of a sphenoid sinus metastasis as a first manifestation of hepatoma, was recently reported by Urvoy et al (4).

The propensity of hepatocellular carcinoma for hematogenous metastases is well known. In two large series (5, 6) of 231 cases of hepatoma, the most frequent sites of metastasis were the lungs, regional lymph nodes, skeleton, and adrenals; less commonly involved were brain, heart, kidney, gallbladder, pancreas, skin, and gastrointestinal tract. There was not a single instance of metastasis to a paranasal sinus (5, 6). Among patients in these two series, only four presented with metastasis as an initial symptom, two with multiple pulmonary metastases and two with pathologic bone fracture (6). A patient showing unusual gingival metastasis from a hepatoma has been reported (7), but examples of "latent" hepatocellular carcinoma manifesting initially as metastases to the spine, skeleton, or brain have long been known (8).

The unusual route of metastasis from the liver to the paranasal sinuses is explained by a hematogenous spread of tumor cells via the paravertebral venous plexus; this system of valveless epidural and paravertebral veins that communicate with the intercostal, azygos, and pelvic veins and venae cavae allows direct dissemination of the tumor to different parts of the body according to changing intrathoracic and intraabdominal pressures. Tumor emboli can thus reach the cranial venous sinuses, with subsequent retrograde spread to the paranasal sinuses.

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Nonmedullary Carcinoma of the Thyroid Gland in Association with Amyloid Goiter: Case Report

ALAN J. LIFTIN, M.D.

Abstract

A case of mixed papillary and follicular carcinoma of the thyroid gland in association with amyloid goiter is presented. The amyloid caused diffuse enlargement of the gland and was found in the stroma of the carcinoma. Medullary carcinoma was not found. The amyloid in the thyroid gland may be secondary to chronic, systemic inflammation in this 53-year-old woman with long-standing rheumatoid arthritis. Although systemic accumulations of amyloid were not documented, chronic renal disease is present and is most likely due to renal amyloidosis. The carcinoma is regarded as an incidental finding unrelated to amyloid deposition in the thyroid gland.

Amyloid goiter is a rare condition in which the thyroid enlargement is due to diffuse deposition of amyloid. Approximately 85 cases have been reported in the world literature (1–15). We recently had the opportunity to study a patient with an amyloid goiter in which a small, papillary-follicular carcinoma was found. This is the first documented case of amyloid goiter with thyroid carcinoma. The patient had rheumatoid arthritis for 14 years. In addition, chronic renal disease was present for 3 years, presumably secondary to renal amyloidosis.

Case Report

A 53-year-old woman developed signs and symptoms of hyperthyroidism. She was found to have a nodular goiter, which was treated with two doses of radioactive iodine. The patient remained euthyroid for approximately 2 years but then noted dyspnea at rest, had stridor and marked thyromegaly, and was again hyperthyroid. Tapazole therapy rendered her hypothyroid, and she was treated with oral thyroid supplements.

Rheumatoid arthritis was diagnosed 14 years prior to surgery, and she was treated with prednisone. She had chronic renal disease of undetermined etiology for 3 years, with the urea nitrogen value approximately 45 mg/100 ml and the creatinine 3.0 mg/100 ml. There was no documented proteinuria or hematuria. A total thyroidectomy was performed 3 years after the first presentation because of an enlarging goiter and pressure symptoms.

The resected thyroid gland weighed 286 gm. The two lobes were symmetrically enlarged and irregularly nodular and the capsule was firm, tan-pink, and focally congested. The usual glistening colloid-containing parenchyma was diffusely replaced by a light pink-tan, waxy tissue. A vague lobular pattern was discernible. A few fluid-filled 2–7 mm cysts were observed, and a 2.0-cm firm, poorly delineated, grey-white area with a stellate configuration was seen in the right lobe (Fig. 1). Histologically, there was almost complete obliteration of the normal thyroid follicular architecture and replacement by an eosinophilic, acellular, hyaline material (Fig. 2). Scattered islands of preserved colloid-filled thyroid follicles and focal, cystically dilated follicles lined

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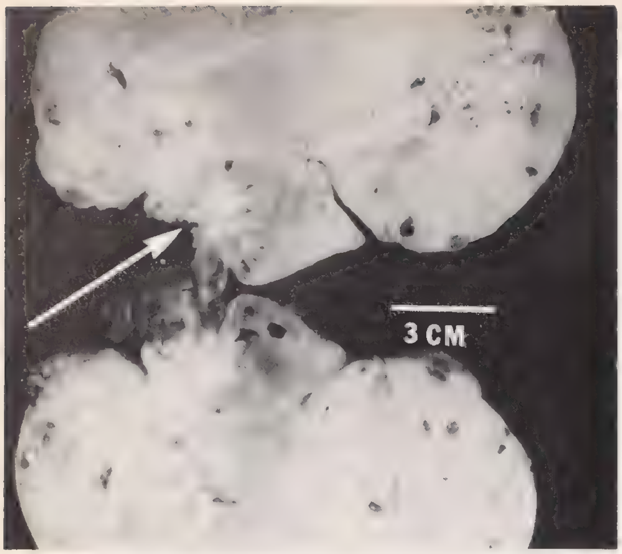


Fig. 1. Bisected right lobe of thyroid showing enlargement and replacement of normal parenchyma by pale, glassy material (amyloid) with cystic foci. Note small, stellate subcapsular papillary carcinoma (arrow).

by low columnar epithelium were observed. The typical brick-red color of amyloid was seen after Congo red staining, and birefringence was demonstrated with polarized light. Fluorescence under ultraviolet light with Thioflavin-T staining and the presence of characteristic fibrils by ultrastructural study confirmed the presence of amyloid. Aggregates of lipocytes were scattered within the amyloid. The grey-white lesion in the right lobe was a mixed papillary and follicular carcinoma with psammoma bodies (Fig. 3). Amyloid deposits were observed within the stroma of the tumor (Fig. 4). Chronic inflammatory cells, including multinucleated foreign-body-type giant cells, surrounded the tumor. The carcinoma was confined to the thyroid gland and there was no evidence of vascular, lymphatic, or capsular invasion.

Discussion

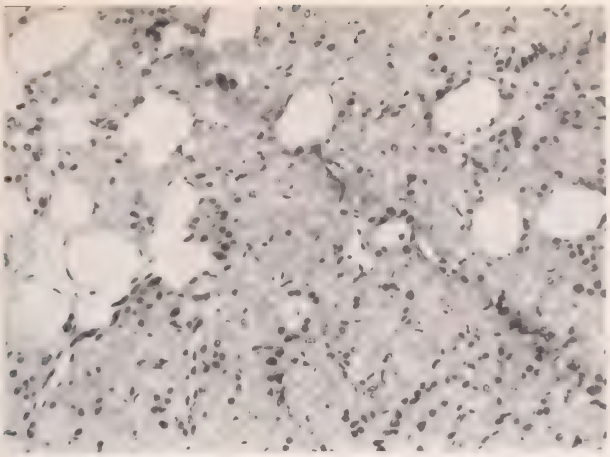
Microscopic deposits of amyloid within the thyroid gland are frequently found in systemic amyloidosis. It is distinctly unusual, however, for amyloid infiltration to be the basis of clinical thyroid enlargement ("amyloid goiter"). Less than 100 reported cases of amyloid goiter were found in a review of the world literature (1–15).

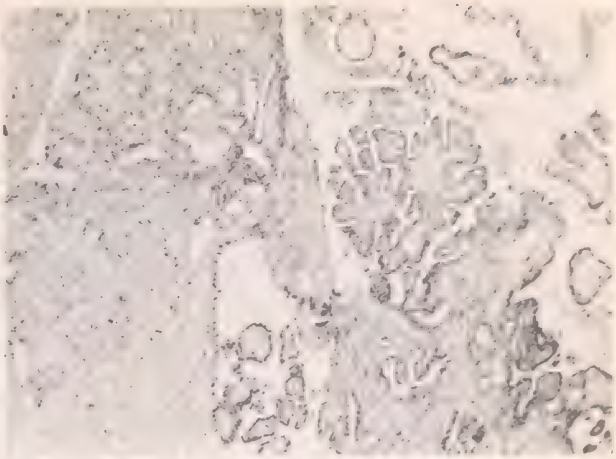
Amyloid goiter usually presents as a rapidly enlarging, firm, nontender, diffusely involved gland which may attain five to ten times the normal size in only a few months. Swelling of the neck is the most common initial complaint. Massive enlargement causing dysphagia, dyspnea, and hoarseness is uncommon. When these occur, they are secondary to pressure effects rather than to infiltration of adjacent structures. Thyroid function is usually not altered, despite extensive amyloid infiltration. Patients are usually euthyroid or mildly hyperthyroid. In most instances, patients with amyloid goiter have systemic amyloidosis, which is often associated with a chronic inflammatory condition such as rheumatoid arthritis (6) or tuberculosis (3).

The diagnosis is seldom made preoperatively and is usually first established by biopsy or thyroidectomy. These procedures are usually performed to rule out malignancy or in order to relieve local symptoms. The gland is diffusely enlarged, irregularly nodular, and firm to hard. The largest amyloid goiter reported weighed 573 gm (3). The parenchyma appears dark-red to tan, nodular or smooth, and focally hemorrhagic. Occasional small cystic spaces filled with colloid are found. Histologically, the normal follicular architecture is completely or almost completely replaced by amyloid. Occasional preserved, often enlarged, distorted follicles containing colloid are seen. Interspersed in the amyloid are clusters of mature adipose cells, scattered lymphocytes and plasma cells, and occasional multinucleated, foreign-body-type giant cells.

Primary malignant tumors of the thyroid gland have been reported to be associated with amyloid deposition. Stromal accumulations of amyloid occur frequently in medullary carcinoma of the thyroid; the nontumorous portion of the gland does not demonstrate amyloid. It has been suggested that the amyloid in medullary carcinoma is synthesized by the tumor cells (16). Stromal amyloid has also been reported in a single case of nonmedullary carcinoma of the thyroid. The amyloid was most striking in the cervical lymph node metastases. Amyloid goiter was not present (17). The case we are now reporting is the first documentation of amyloid goiter in association with a primary thyroid neoplasm. Since the tumor involved only a minor portion of one lobe, its association with widespread amyloid deposition in the gland appears to be incidental rather than related.

Amyloid goiter is most frequently found in patients with systemic amyloidosis. However, in a few cases amyloid cannot be demonstrated outside the thyroid gland. These are classified as primary localized amyloidosis of the thyroid (11). Our patient has a chronic inflammatory condition





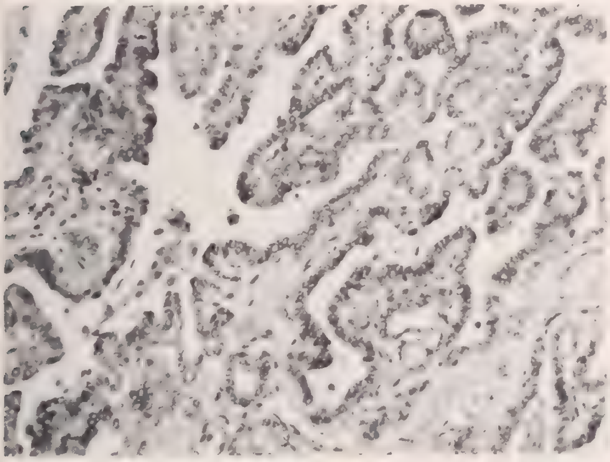


Fig. 2. **Top left** Thyroid parenchyma replaced by amyloid. Foci of mature lipocytes are noted (hematoxylin and eosin, original magnification, ×250).

Fig. 3. **Top right** Transition zone showing papillary carcinoma (**right**) and adjacent thyroid replaced by amyloid (**left**) (hematoxylin and eosin, original magnification, ×100).

Fig. 4. **Left** Papillary thyroid carcinoma with stromal amyloid (hematoxylin and eosin, original magnification, ×250).

which predisposes to the development of secondary amyloidosis. The history of chronic renal disease is probably related to amyloid infiltration of the kidneys. However, this diagnosis was not established, and we cannot rule out the possibility that the amyloid is isolated to the thyroid gland.

Acknowledgments

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Laparoscopy for Gastrointestinal Diseases

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Abstract

The laparoscope is an important diagnostic and therapeutic tool in the management and treatment of gastrointestinal diseases. The authors' personal experience includes 165 consecutive laparoscopic examinations over a 3-year period. Local anesthesia was employed in 150 patients. The diagnostic accuracy was 95% for acute abdominal pain syndromes, 93% for ascites of unknown etiology, 92% for abdominal masses, 91% for focal liver disease, and 43% for chronic abdominal pain syndromes. Sixteen patients had nondiagnostic percutaneous biopsy or aspiration. In all these patients definitive diagnosis was made at laparoscopy. The morbidity rate was 1.8%. These data indicate that laparoscopy is a highly accurate diagnostic modality in a wide range of gastrointestinal disorders.

Laparoscopy is a diagnostic and therapeutic tool ideally suited for many gastrointestinal diseases. Recent technical improvements in the fiberoptic illumination system allow precise visual documentation of intraabdominal pathology. Sophisticated biopsy instruments permit definitive histologic confirmation of both malignant and benign processes. This allows better patient selection for laparotomy and increases the therapeutic yield of exploratory surgery.

This report reviews the authors' personal experience with laparoscopy used solely for the diagnosis and treatment of gastrointestinal diseases.

Material

Between December 1981 and March 1984, 165 consecutive laparoscopic examinations were performed by the authors at The Mount Sinai Hospital. The age of the patients ranged from 14 to 91 years with a mean of 44 years. There were 98 females and 67 males. Thirty-eight percent of the patients had had previous surgery (Table 1). Table 2 describes the categories of disease for which laparoscopy was undertaken and the number of patients in each group. Local anesthesia was employed in 150 patients (91%) and general anesthesia in the remaining 15 patients.

Technique and Equipment

The authors use the technique described by Boyce and Palmer for induction of the pneumoperitoneum and insertion of the laparoscope (1). After sterile preparation of the abdominal wall, local-anesthesia field block with 0.5% lidocaine is used routinely. However, if the patient is very young or uncooperative, general anesthesia is recommended. Nitrous oxide is the insufflating gas of choice when performing the procedure under local anesthesia, as it does not cause irritation of the parietal peritoneum. Infiltration of

TABLE 1
Number of Patients Who Had Previous Surgery

No. of operations	No. of patients
1	36
2	19
3	6
4	1

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TABLE 2
Reason for Laparoscopy and Number of Patients in Each Category

Indication	No. of patients
Focal liver pathology	44
Abdominal pain, acute and chronic	42
Ascites of unknown etiology	30
Abdominal mass	25
Prelaparotomy, second look	12
Lymphoma	11
Miscellaneous	1
	165

TABLE 3
Type of Liver Pathology Histologically Confirmed

Malignant	No. of patients	Benign	No. of patients
Adenocarcinoma 1° unknown	7	Macronodular Cirrhosis	3
Hepatocallular Ca	5	Cyst*	4
Colon Ca	4	Fibrosis	2
Pancreatic Ca	3	Steatosis	1
Breast Ca	1	Abscess	
Gastric Ca	1	Pyogenic	1
Leiomyosarcoma	1	Amebic	1
Lung Ca	1	Hemangioma*	1
Melanoma	1	Adenoma	1
Squamous cell Ca	1		
Histocytic medullary reticulosis	1		

* Biopsy contraindicated.

all layers of the abdominal wall is mandatory for a painless procedure. A 1-cm skin incision is made 2.5 cm above and to the left of the umbilicus if the pathologic process is located in the upper abdomen. Other sites may be used depending on the location of pathology (1). It is best to avoid the area of the ligamentum teres and the inferior and superior epigastric vessels. The incision should be at least 2.5 cm from any previous abdominal scar.

The R. Wolf 2043.50 insufflation device is used for delivery of gas into the peritoneal cavity via the Verres pneumoperitoneum needle. The Olympus 0° rigid fiberoptic laparoscope provides exceptional visual acuity and is used routinely. The Olympus OM-2 35-mm SLR camera with OM-12 endoscopic screen and the Olympus SM-EFR lens adaptor with cable attachment to the Olympus CLE-F light source provides completely automatic exposure capability with near-perfect photographic documentation. Kodak Ektachrome 400 ASA film is used routinely. The Olympus LS-2 lecturescope provides a method for resident training with direct supervision.

Results

Focal Liver Disease. All patients had focal liver defects on either CT scan, liver-spleen scan, or sonogram. Table 3 lists the histologically confirmed pathology obtained by directed laparoscopic liver biopsy. Eleven patients had previous nondiagnostic percutaneous blind biopsies. The diagnosis was secured in all those patients by laparoscopic directed biopsy. The patient with the amebic abscess had aspiration and drainage performed laparoscopically. Of the 44 patients, a definitive diagnosis was made in 40 (91%). The false-negative laparoscopies included two patients with extensive adhesions that precluded adequate visualization and two patients who had lesions not on the surface. All four patients required laparotomy for definitive diagnosis.

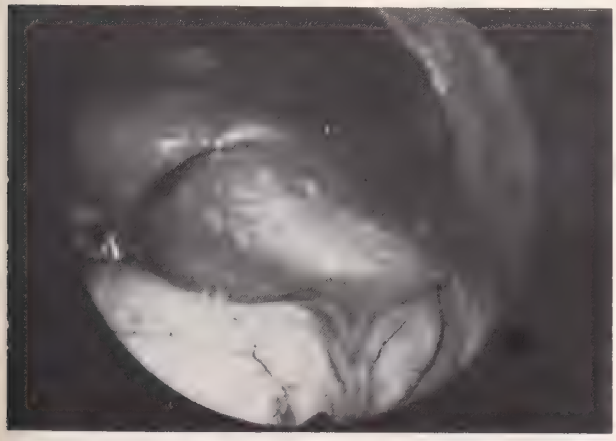
Fig. 1. Enlarged left lobe of liver with multiple metastatic deposits. Stomach in foreground with peristaltic wave seen.

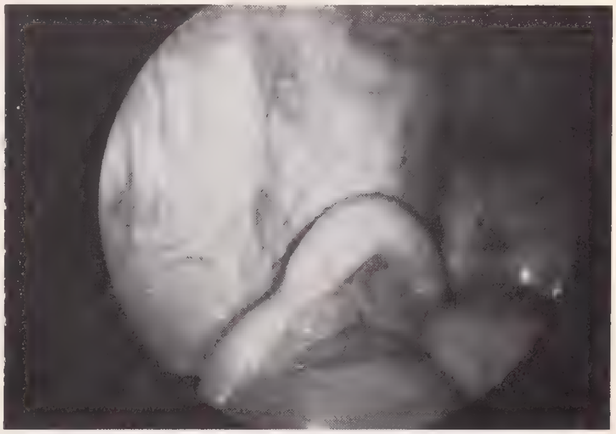
Fig. 2. Laparoscopic view of a normal appendix with mesoappendix seen. Terminal ileum in foreground and cecum in background.

TABLE 4
Pathology of Acute Abdominal Pain Determined by Laparoscopy

Gynecologic infection	6
Appendicitis	5
Cholecystitis	2
Crohn's disease	1
Diverticulitis	1
Ovarian cancer	1
Acute enteritis	1
Ruptured spleen	1
Porphyria	1
Vasculitis	1

Figure 1 demonstrates the laparoscopic view of metastatic colon carcinoma in the left lobe of the liver.

Acute Abdominal Pain. Twenty-one patients had acute abdominal pain syndromes. All patients had localized peritoneal findings. Only patients presenting a real diagnostic problem underwent laparoscopy. Table 4 lists the pathological states present. A definitive diagnosis was possible in 20 patients (95%). The one false-negative case was in a patient with right lower quadrant pain. The appendix was retrocecal, and therefore not visualized. A laparotomy revealed a normal appendix. The patient with porphyria had atypical peritoneal findings. Laparoscopy was completely normal (Fig. 2). Elevated porphyrins were confirmed the next day.

Chronic Abdominal Pain. Out of the total of 165 patients, 21 patients with chronic abdominal pain syndromes underwent laparoscopy. All patients had negative or equivocal extensive prelaparoscopic evaluation. Definitive diagnosis was possible in nine patients (43%). Table 5 lists the different pathologic states confirmed by laparoscopy. The two patients with pain secondary to adhesions were dramatically helped by laparoscopic lysis. Both patients with signs of previous appendicitis had appendectomies and have remained asymptomatic. The two patients with Crohn's disease had multiple nondiagnostic upper gastrointestinal radiographs. Laparoscopy was definitive (Fig. 3).

TABLE 5
Pathology of Chronic Abdominal Pain Determined by Laparoscopy

Adhesions	2
Crohn's disease	2
Chronic appendicitis	2
Pancreatitis (subacute)	1
Pelvic inflammation	1
Intestinal ischemia	1

Ascites of Unknown Etiology. Thirty patients with exudative ascites of unknown etiology underwent laparoscopic examination. Definitive diagnosis was possible in 28 cases (93%). All patients had nondiagnostic prelaparoscopic paracentesis. Table 6 catalogues the causes histologically confirmed. Two patients had false-negative results. Both patients required laparotomy for definitive diagnosis.

Abdominal Mass. Twenty-five patients were evaluated by laparoscopy (Table 7). Definitive diagnosis was possible in 23 (92%). The two false-negative cases were both pancreatic carcinoma and required laparotomy. Six patients had nondiagnostic Chiba needle aspirations prelaparoscopy. All these patients had positive laparoscopic-guided biopsies. Of note are five patients with retroperitoneal non-Hodgkin's lymphoma who had

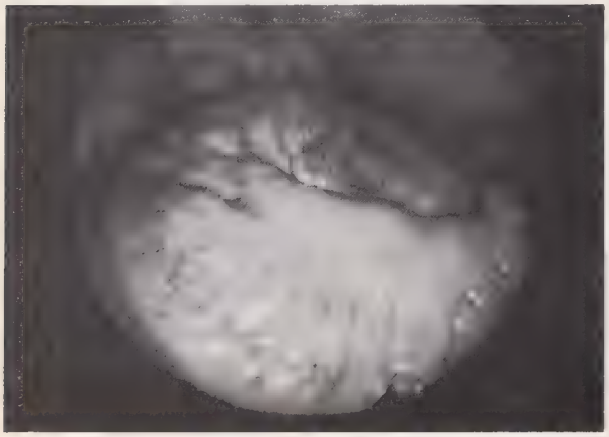
Fig. 3. Typical Crohn's disease involvement of terminal ileum. Note "creeping" mesenteric fat and enlarged mesenteric lymph nodes.

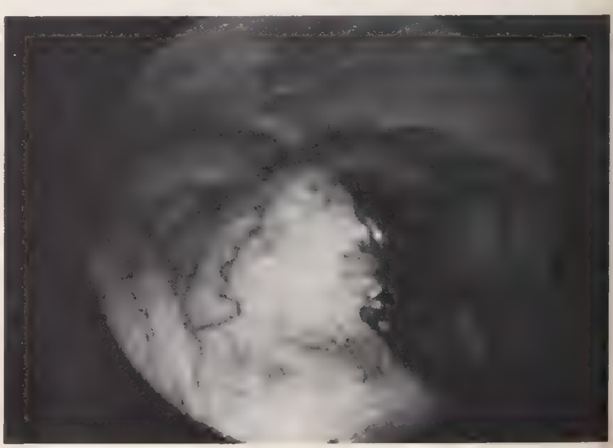
Fig. 4. Massively enlarged retroperitoneal lymph nodes pushing small bowel away in background. Omentum is to the left. Note biopsy site.

TABLE 6

Pathology of Ascites of Unknown Etiology Determined by Laparoscopy

Malignant		Benign	
Carinomatosis	9	Cirrhosis	8
Ovarian Ca	6	Vasculitis	1
Mesothelioma	2		
Myelofibrosis, liver	2		
Hepatoma	1		
Pancreatic Ca	1		

TABLE 7

Pathology of Abdominal Mass Determined by Laparoscopy

Malignant		Benign	
Adenocarcinoma	8	Diverticular phlegmon	1
Non-Hodgkin's lymphoma	5	Crohn's disease	1
Pancreatic Ca	3	Intrahepatic GB	1
Lymphosarcoma	1	Subacute GB	1
Spindle cell sarcoma	1	Splenic cyst	1
		Leiomyoma, stomach	1
		No mass	1

positive biopsies laparoscopically (Fig. 4). Definitive treatment of the patient with the benign splenic cyst was drainage and creation of a cyst-peritoneal window laparoscopically.

Prelaparotomy or Second Look. Twelve cancer patients underwent laparoscopy either to determine resectability or evaluate chemotherapy treatment, or to identify a cause for a rising CEA (Table 8). Laparoscopy yielded helpful information in 8 of the 12 patients. A needless laparotomy was avoided in three patients.

Discussion

There are six common indications for laparoscopy in gastrointestinal diseases:

- Focal defects in the liver.
- Abdominal masses.
- Determining etiology of abdominal pain.
- Ascites of unknown etiology.
- Determining operability of intraabdominal neoplasms.
- Evaluating intraabdominal trauma.

To attain high diagnostic rates, a thorough understanding of normal and morbid anatomy is required. A positive laparoscopy is defined as a histologically proven pathologic entity obtained on directed biopsy, a beneficial therapeutic result, or visual documentation of an inflammatory process. Using these criteria, 141 of 165 laparoscopies were positive (85%). If the category of chronic abdominal pain is not included, the rate of positivity increases to 91%. All 11 nondiagnostic percutaneous liver biopsies and all six skinny-needle aspirations were positive laparoscopically.

Many pathologic retroperitoneal processes are not visible and, therefore, not approachable laparoscopically. However, if retroperitoneal pathology extends into the greater sac, visualization and biopsy are possible. This occurred in five patients with non-Hodgkin's lymphoma. Several authors have described directed biopsy of pancreatic lesions via the lesser omentum (2, 3). There are both absolute and relative contraindications to laparoscopy (Table 9). Note that 38% of the patients in this series had had previous surgery.

Although laparoscopy is mainly a diagnostic tool, significant therapeutic benefit is possible in selected cases. Two patients with abdominal pain secondary to adhesions were significantly helped by lysis laparoscopically. One patient had aspiration and drainage of a hepatic amebic abscess (Fig. 5). Another patient with a symptomatic splenic cyst had aspiration and creation of a cyst-

TABLE 8

Findings of Prelaparotomy or Second-Look Laparoscopy

	Disease	Reason	Remarks
1.	Ca stomach	?Carcinomatosis	None found; gastrectomy
2.	Ca stomach	Multiple defects on scan	+Liver metastases; no surgery
3.	Recurrent colon Ca	Single-lung metastasis	Liver metastases; lobectomy
4.	Recurrent colon Ca	Rising CEA	Negative examination; no surgery
5.	Ca lung	Liver defect on scan	Focal steatosis; no surgery
6.	Recurrent colon Ca	Pelvic recurrence	Not seen because of adhesions
7.	Recurrent colon Ca	Evaluation of chemotherapy	No change; chemotherapy continued
8.	Recurrent colon Ca	Evaluation of chemotherapy	Perforation; laparotomy
9.	Recurrent colon Ca	Rising CEA	No tumor seen; pelvic recurrence 3 months later
10.	Esophageal Ca	Liver metastases	No tumor seen; laparotomy
11.	Recurrent colon Ca	Rising CEA	No tumor seen; no surgery
12.	Ulcerative colitis—colon Ca	Evaluation of treatment	No tumor seen; chemotherapy stopped

TABLE 9

Contraindications to Laparoscopy

Absolute	Relative
1. Generalized peritonitis	1. Multiple previous abdominal procedures
2. Intestinal obstruction	2. Uncooperative patient
3. Abdominal wall infection	
4. Uncorrectable coagulopathy	

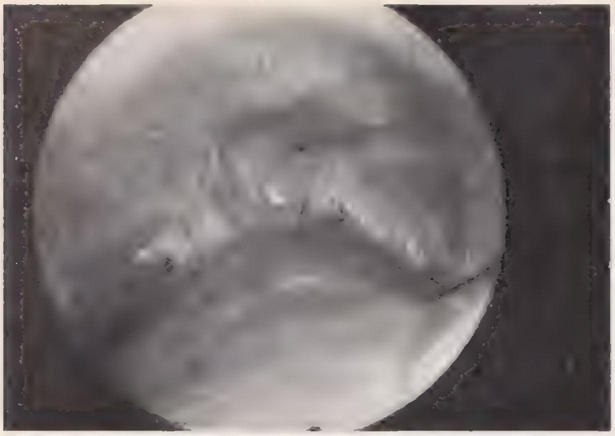

Fig. 5. Amebic abscess at dome of right lobe of liver. Adhesions fixing abscess to right hemidiaphragm.

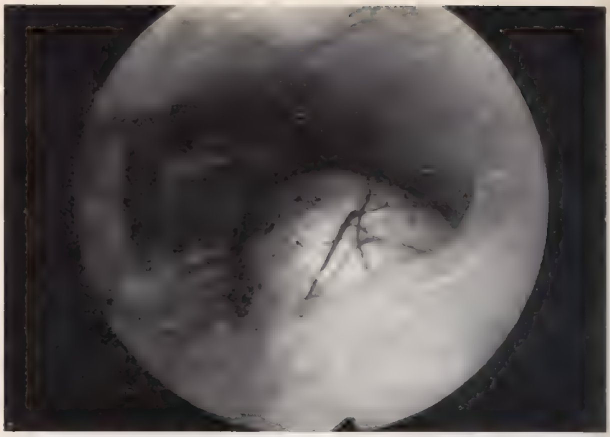

Fig. 6. Splenic cyst. Note avascular areas easily seen. Left hemidiaphragm visible in background and normal colodiaphragmatic attachment in foreground.

peritoneal window preventing reaccumulation (Fig. 6).

The morbidity and mortality rates are minimal if the proper contraindications are observed and if the procedure is performed with local anesthesia. The largest review is by Bruehl, who studied 63,845 laparoscopies performed by 67 physicians (4). He reports 1,594 complications with 19 deaths, or a mortality rate of 0.029%. Similar statistics have been reported by Vilardell et al in a survey of 1,455 examinations with two deaths (0.13%) (5). The three complications in this series included subcutaneous emphysema, a colonic perforation that required immediate laparotomy for repair, and delayed bleeding from a liver biopsy.

In summary, laparoscopy is a highly accurate diagnostic procedure for many gastrointestinal diseases. In addition, significant therapeutic benefit is possible in selected patients. The procedure may be accomplished with minimal morbidity.

Acknowledgments

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1. You CH, Lee KY, Chey RY et al. Electrogastrographic study of patients with unexplained nausea. Gastroenterology 1980; 79:311–314.

2. Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr., Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–472.

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Clinical Epidemiology

Michael N. Mulvihill, Dr.P.H., and
Mary Louise Skovron, Dr.P.H.
Guest Editors

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Vol. 52
Number 4
April 1985

CONTENTS

CLINICAL EPIDEMIOLOGY

Introduction *Michael N. Mulvihill, Dr.P.H., and Mary Louise Skovron, Dr.P.H.* ... 234

EPIDEMIOLOGY AT MOUNT SINAI SCHOOL OF MEDICINE

Perspective *Kurt W. Deuschle, M.D.* ... 237

Clinical and Obstetric Risk Factors for Preterm Delivery *Gertrud S. Berkowitz, Ph.D.* ... 239

Rubella Susceptibility among Prenatal and Family Planning Clinic Populations *Sally Faith Dorfman, M.D., MSHSA, and Charles H. Bowers, Jr., M.D.* ... 248

Tuberculosis Chemoprophylaxis for Diabetics: Are the Benefits of Isoniazid Worth the Risk? *David N. Rose, M.D., Alan L. Silver, M.D., MPH, and Clyde B. Schechter, M.D.* ... 253

Some Effects of a Hospital Employee Strike on Patient Satisfaction *Gary Rosenberg, Ph.D., Edward J. Speedling, Ph.D., Helen Rehr, D.S.W., and Barbara J. Morrison, D.S.W.* ... 259

Should Mild Hypertension Be Treated? An Attempted Meta-Analysis of the Clinical Trials *Henry S. Sacks, Ph.D., M.D., Thomas C. Chalmers, M.D., A. Ancona Berk, Ph.D., and Dinah Reitman, M.P.S.* ... 265

Factors Predicting Survival for Six Months after Cardiopulmonary Resuscitation: Multivariate Analysis of a Prospective Study *Mary Louise Skovron, Dr.P.H., Emanuel Goldberg, M.D., and Kasja Suljaga-Petchel, M.D., M.P.H.* ... 271

Patterns of Diazepam Prescribing in Primary Care: A Case Control Study *Michael N. Mulvihill, Dr.P.H., Kasja Suljaga-Petchel, M.D., M.P.H., Jane Falkenstein, M.D., and Azimah P. Ehr, M.D., M.P.H.* ... 276

continued

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CONTENTS *continued*

EDUCATION IN COMMUNITY MEDICINE

Perspective *Bessie S. Dana, M.S.S.A.* 282

Primary Care of Elderly Women: Is Pap Smear Screening Necessary? *Jeanne S. Mandelblatt, M.D., and David D. Hammond, M.D.* 284

The Prevalence of Alcoholism in Acute-Care General Hospital Patients *Pearl Lefkowitz, M.D., and Kasja Suljaga-Petchel, M.D., M.P.H.* 291

Error Rate Factor in the Management of Suspected Acute Appendicitis: Has Anything Changed? *Anne M. Mockapetris, B.A.* 297

Refusal of Treatment: The Role of Psychiatric Consultation *Madeleine Stam, B.A., and James J. Strain, M.D.* 306

Clinical Epidemiology

The Mount Sinai Journal of Medicine
Vol. 52, No. 4, April 1985
Printed in U.S.A.

Clinical Epidemiology

Introduction

Michael N. Mulvihill, Dr.P.H., and Mary Louise Skovron, Dr.P.H.

Epidemiology is frequently defined as the study of the determinants and distributions of states of health and disease in populations. Within this discipline, clinical epidemiology is epidemiologic research of "immediate interest to physicians and clinical investigators" (1). The areas of application can be preventive, diagnostic, or therapeutic, in any combination.

While the idea that the cause of diseases can be discerned by careful observations of the environments and persons in which they occur can be traced back to Hippocrates (2), the systematization of the epidemiologic method was a feature of the development of the scientific method. Just as physical phenomena were lawful, so were biological phenomena, and specifically the manifestations of disease in population groups. The laws governing these phenomena were discernible through inductive reasoning and demonstrable by experiment.

During the period in the nineteenth century referred to by Lilienfeld as the "greening of epidemiology" (3), when the epidemiologic method was being formalized, the method was put to use to develop and test competing hypotheses to explain the most troublesome diseases of the time. John Snow, for example, reasoned and demonstrated by observational studies ("natural experiments") that cholera was caused by an organism and was usually transmitted by contaminated drinking water (4). The great epidemiologic work of this period is mainly associated with advances in knowledge of the epidemic infectious diseases, then the major causes of morbidity and mortality.

Among the forerunners of nineteenth-century research in clinical epidemiology was James Lind, who through epidemiologic reasoning developed a theory for the cause of scurvy and experimentally demonstrated in 1747 that this disease could be cured by a diet of citrus fruits (5).

Although the efficacy and safety of various treatments for disease is a logical part of clinical epidemiology, clinical epidemiologists, by studying groups of patients encountered in clinical practice, can further some of the "clinical" goals of epidemiology, the investigation of disease causality. For example, in recent times, Herbst and co-workers in Boston were led to investigate clear-cell carcinoma of the vagina in young women and demonstrated its very strong association with prenatal DES exposure (6).

The current position of epidemiology as a cornerstone of public health practice is widely accepted. Epidemiologists have traditionally played a central role in the study of disease outbreaks, investigations of the etiology and natural history of specific conditions, assessment of the efficacy of preventive interventions, community diagnosis, and the planning and evaluation of health services and systems. Indeed, epidemiology is the basic science of public health, preventive medicine, and community medicine.

In recent years epidemiology has assumed a role of increasing importance in the clinician's activities. As participants indicated during the often cited Fogarty Center Conference (7), the ability to employ biostatistical and epidemiologic techniques (or at least to critically assess the appropriateness and validity of their use) has become an essential element of effective clinical practice and research. Epidemiologic data and techniques contribute significantly to the proper choice and

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interpretation of diagnostic and therapeutic methods, to estimation of survival, and to assessment of the probable prognosis associated with each therapeutic option. Competence in the epidemiologic method is crucial in the design and interpretation of meaningful clinical research.

Existing schools of public health do an admirable job of training individuals whose focal interest is the practice of epidemiology. For practitioners whose primary focus remains clinical, however, the medical school is the most appropriate setting for training in epidemiologic and statistical methods. Medical schools such as Mount Sinai, situated within major medical centers and affiliated with universities, have as their focus the provision of clinical care in a multidisciplinary environment. In the medical center, students and residents enjoy the familiarity of the clinical setting and the continuity of clinical activities while studying epidemiology and biostatistics, as well as direct access to sites for clinical investigations—an ideal milieu for training in and practice of clinical epidemiology.

The articles in this issue illustrate the breadth of applications of the epidemiologic method. Several clinical departments are represented, and a variety of clinical issues are addressed. The characteristic all the articles share is that each is an application of the epidemiologic method.

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Epidemiology at Mount Sinai School of Medicine

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Epidemiology at Mount Sinai School of Medicine

Perspective

KURT W. DEUSCHLE, M.D.

When the Mount Sinai Medical School opened its doors to students in 1968, concern for the health of population groups was at the core of its educational philosophy. With Dr. George James as its first president and dean, a public health approach to medicine was guaranteed. Indeed, the Department of Community Medicine was defined as the academic discipline concerned with the identification and solution of health problems in population groups. The faculty assembled to carry out this academic program was multidisciplinary, ranging from clinicians with societal interests to anthropologists, epidemiologists, health economists and planners, environmental scientists, nurses, social workers, and sociologists.

While there was a mixture of public health scientists, there was also a need to identify a common, useful, and binding intellectual problem-solving approach. This was found in the discipline of epidemiology, the science and methodologic approach to diagnosing, treating, and preventing health problems in population groups. There are, of course, many definitions of epidemiology. I have selected the definition in *A Discursive Dictionary of Health Care* (Subcommittee on Health of the Committee on Interstate Commerce, US House of Representatives 1976): "the study of the nature, cause, control and determinants of the frequency and distribution of diseases and disability in human populations." Defining health issues in population terms was considered so vital and potentially so universally applicable as a scientific methodological tool that, instead of establishing a separate division of epidemiology, the Epidemiologic Core Unit (the "epi-unit" in the affectionate chat of the faculty) was established in the Education Office. The Education Office cuts across the entire department and it is the integrating network for the academic life of our Community Medicine Department.

The integrated faculty teach the basic undergraduate courses in epidemiology. Both the new and veteran faculty members are upgraded and enriched in their skills in epidemiology by the professional epidemiologists in the department. The residents and fellows participate in a special seminar series and also participate in the first-year epidemiology and biostatistics course and the community medicine clerkship teaching program.

In addition to the educational activities, a research seminar series known as the epidemiology network has been established. The group, which includes epidemiologists from other institutions, provides consultation to any faculty member or postgraduate student who is proposing a population study or seeking a critical analysis of work in progress, an exciting intellectual forum for ideas on epidemiologically oriented investigations.

Another spin-off of the Epidemiological Core Unit has been the plan to establish an epidemiologic field station in each of our hospital affiliates. Thus far only one field site, Beth Israel Medical Center, has had continuous epidemiologic input available over the past 10 years. There are

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ambitious plans to extend the affiliated hospital epidemiology units but funding problems have stalled this effort.

The Department of Community Medicine has identified technical assistance as the major community medicine "practice" or service. The role of epidemiologists in the multidisciplinary teams that provide technical assistance to The Mount Sinai Hospital and our affiliated institutions, to East Harlem community groups, and to international organizations as well, has been exemplary. Numerous research projects have coupled clinical investigators with our epidemiologists as partners in a population-oriented research enterprise. This same population-based approach has been applied to the improvement of health services with our hospital associates, East Harlem and other NYC community groups, and especially with international cross-cultural clients. We find that again the epidemiological problem-solving methodology is one of the basic tools which facilitates effective technical assistance.

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Clinical and Obstetric Risk Factors for Preterm Delivery

GERTRUD S. BERKOWITZ, PH.D.

Abstract

Possible clinical and obstetric risk factors of preterm delivery were evaluated for 175 mothers of singleton preterm infants and 313 mothers of singleton term infants who delivered at Yale-New Haven Hospital between January 1977 and January 1978. Gestational age was assessed by Dubowitz examination. Sociodemographic and obstetric data were obtained from structured interviews of the mothers and from hospital delivery records. The following factors were found to be significantly associated with preterm delivery: low socioeconomic status, low pregravid weight, inadequate weight gain during the pregnancy, previous preterm delivery, history of infertility problems, history of an induced abortion, vaginal spotting or light bleeding during the pregnancy, antepartum hemorrhage and placental abnormalities, urinary tract infection during the latter part of the pregnancy, and incompetent cervix.

Despite advances in antenatal diagnosis and management, the incidence rate of preterm delivery has remained virtually unchanged over the last few decades (1, 2). Furthermore, while neonatal survival has improved considerably (3–6), preterm infants still run a high risk of neonatal morbidity and mortality (7–10).

The term "prematurity" has now been replaced by "low birth weight" to describe an infant weighing less than 2,500 grams, and by "preterm" to characterize a baby born before 37 weeks of gestation (11). Yet, most epidemiological studies have continued to emphasize the birth weight parameter (12, 13). In order to elucidate the risk factors specific to gestational prematurity, an epidemiologic case-control study of preterm delivery was undertaken at Yale-New Haven Hospital.

Previous reports have described the overall findings of this investigation (14) as well as the findings concerning the effects of such environmental factors as cigarette smoking, alcohol consumption, caffeine intake (15), physical activity (16), and psychosocial stress (17). This report will focus on clinical and obstetric risk factors of preterm delivery and will consider results that have not been previously presented.

Materials and Methods

The overall design of the study involved comparing characteristics of mothers of preterm infants (the cases) to characteristics of mothers of term infants (the controls). The cases were defined as women who delivered singleton live births before 37 weeks of gestation during the period January 1977 to January 1978. Preterm deliveries that were not preceded by spontaneous labor or spontaneous rupture of the membranes were not included, as the timing of such deliveries was due to obstetric intervention. Women who were referred from outlying areas were also excluded since their sociodemographic characteristics were found to differ from those of patients drawn from Greater New Haven.

The controls were women who delivered singleton live births at 37 weeks of gestation or later. A 10% random sample of all singleton de-

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liveries during the same time period as the cases was used to identify potential controls.

The Dubowitz score (18), which is based on selected neurologic and physical characteristics of the neonate, was used to determine the gestational ages of all infants. All examinations except those for about 100 newborns were performed by the author. The remaining Dubowitz examinations were conducted by an examiner trained by the author. A test of interobserver reliability in the scoring of 10 babies showed perfect agreement between the two examiners in the assignment of preterm or term status.

Premature rupture of the membranes was defined for the purpose of this study as (a) spontaneous rupture of the membranes 12 or more hours prior to delivery for term deliveries, and (b) spontaneous rupture of the membranes anytime before the onset of labor or, where labor did not occur, before surgical delivery in the case of preterm deliveries.

Women were eligible for the study if they (a) could be interviewed during their postpartum stay in the hospital, (b) spoke English, and (c) had not placed their babies for adoption. As a result, 28 potential cases and 37 potential controls were not interviewed. Also, 22 cases and 2 controls could not be included because a Dubowitz examination could not be performed or the mothers were regarded as too ill or emotionally distressed to be interviewed. In addition, 6 cases and 14 controls refused to participate in the study. Interviews were completed on 175 cases and 313 controls; this represents a response rate of 86.2% for the cases and 95.1% for the controls. No systematic differences in age, race, or marital status were apparent between the cases and controls who participated in the study and those who were excluded.

Data regarding sociodemographic and medicoobstetric characteristics of the women were obtained from a structured, standardized questionnaire. Hospital delivery records were also abstracted for relevant information.

Characteristics of cases and characteristics of controls were initially compared one at a time and were tested for statistical significance by contingency chi-square and Student's *t*-tests. Fisher's exact test was substituted for the chi-square test when tables contained small numbers in certain categories. Since it was also desired to examine the effect of one variable while controlling for the effects of others, log linear (19) and linear logistic (20) models were used to consider several factors simultaneously. From all the preceding procedures, odds ratios could be calculated. The odds ratios, which approximate the relative risk, indicate the increase or decrease in the risk of a preterm delivery to women exposed as compared to women not exposed to a certain factor. For instance, an odds ratio of 2 implies that a woman exposed to a risk factor is twice as likely to deliver a preterm infant as a woman not exposed to the risk factor.

Results

The mean gestational age was 34.1 weeks for the cases and 39.8 weeks for the controls, and the mean birth weight was 2,067 grams for the infants of the cases and 3,430 grams for the babies of the controls. Seventy-six percent of the preterm and 1.6% of the term infants weighed 2,500 grams or less. Using the Colorado birth weight percentiles (21), 5.7% of the infants of the cases and only 1.3% of the infants of the controls fell below the 10th percentile for weight. Premature rupture of the membranes was recorded for 74 (43.8%) of the cases as compared to 49 (16.3%) of the controls.

When compared to the controls, the cases were more likely to be young, unmarried, and of low socioeconomic status (Table 1). The case group also contained proportionately more black women than the controls, but the difference was not statistically significant. The cases had a significantly lower pregravid weight than the controls. While the average height was slightly lower for the cases than the controls, the case group actually had a deficit of both very short (≤60″) and moderately tall (>66″) women. When weight was corrected for height (weight/height), it was found that the cases were only moderately lighter for height than the controls.

Assessment of the patients' menstrual history (Table 1) revealed that the cases had reached menarche at a younger age and tended to have experienced more irregularity of cycles in the year before the pregnancy than had the controls. Although the difference was not statistically significant, the cases also reported more metrorrhagia before the pregnancy than the controls, even after oral contraceptive users and IUD users were excluded.

Case-control comparisons of the patients' pregnancy history (Table 2) showed that the proportion of primiparas was similar for cases and controls, but that the proportion of primigravidas was considerably higher for the controls than the cases. The reason for this contrast is apparent when examining the outcome of the penultimate pregnancy; the cases had slightly higher percentages of stillbirths and spontaneous abortions and

TABLE 1

Distribution of Cases and Controls by Selected Maternal Characteristics, Tests of Statistical Significance, and Odds Ratios

Characteristic	Cases % (n = 175)	Controls % (n = 313)	Statistical test	Odds ratio	95% Confidence intervals
Age (years)					
14–17	8.6	5.4			
18–19	12.6	8.3		1.8	
20–24	26.8	20.4	χ^2_5 = 9.53	(women under vs.	1.2, 2.6
25–29	32.0	40.3		women over age 25)	
30–34	16.0	21.4			
35–41	4.0	4.2			
Marital status					
Married	64.0	77.3		2.2	
Divorced	1.7	2.2	χ^2_1 = 11.66**†	(never vs. ever	1.4, 3.3
Separated	2.3	2.6		married women)	
Never married	32.0	17.9			
Race					
White	65.7	72.8		1.4	
Black	29.1	22.7	χ^2_1 = 2.34‡	(black vs. white	0.9, 2.2
Hispanic	4.0	3.2		women)	
Other	1.2	1.3			
Socioeconomic status§					
Class I (upper)	6.3	13.1			
Class II (upper mid)	8.0	14.7		3.3	
Class III (middle)	18.9	21.1	χ^2_4 = 15.78**	(Class V vs. Class	1.6, 7.0
Class IV (lower mid)	33.7	30.0		I women)	
Class V (lower)	30.3	19.2			
Unknown	2.8	1.9			
Mean height (inches)	63.8	64.1	t_{485} = −1.2		
Mean pregravid weight (pounds)	124.9	133.3	t_{411} = −3.53**		
Mean age at menarche (years)	12.4	12.7	t_{481} = −2.03*		
Mean range between shortest and longest cycle in year before pregnancy (days)	8.9	6.4	t_{460} = 1.96 (p = 0.051)		

Unknowns were excluded from analysis.

* $p < 0.05$.

** $p < 0.01$.

† Divorced and separated women excluded from calculation of χ^2 test and odds ratio.

‡ Hispanic and "other" groups excluded from calculation of χ^2 test and odds ratio.

§ Socioeconomic status classified by Hollingshead's two-factor index of social position (22).

twice as high a proportion of induced abortions as the controls. Only two women in the sample reported a prior ectopic pregnancy and both of these were controls.

The repetitiveness of preterm deliveries is evident in Table 2. When analysis was limited to the last live birth, only 3% of the controls as compared to 42.7% of the cases reported that their previous delivery had taken place before 37 weeks. Similarly, when all previous livebirths were considered, 4.3% of the controls but 50% of the cases reported at least one previous preterm delivery.

A statistically significant association was found between dilatation and curettage procedures (exclusive of induced abortions) and preterm delivery (Table 3). The proportion of patients who had had an operation on their cervix, uterus, or vagina was also significantly higher for the cases than for the controls (Table 3). Using the generally accepted clinical definition of infertility as the inability to conceive after a year of trying (23), close to twice as many cases as controls were classified as having had a history of infertility problems (Table 3).

In general, the cases reported higher rates of pregnancy complications than did the controls (Table 4). Specifically, the cases had a statistically significant excess of urinary tract infections during the second and third pregnancy trimesters, spotting or light bleeding during all three trimesters, and heavy bleeding during the second and third trimesters. The hospital delivery records also showed that the cases were significantly

TABLE 2

Distribution of Cases and Controls by Pregnancy History and Odds Ratios

Characteristic	Cases % (n = 175)	Controls % (n = 313)	Odds ratio	95% Confidence intervals
Pregnancy order				
1	26.3	38.3	1.7 (multigravidas vs. primigravidas)	1.2, 2.6
2	35.4	31.6		
3	21.7	15.7		
4	9.7	8.0		
5+	6.9	6.4		
Birth order				
1	45.1	47.6	1.1 (multiparas vs. primiparas)	0.8, 1.6
2	36.0	30.7		
3	12.0	12.5		
4	4.6	7.3		
5+	2.3	1.9		
Outcome of penultimate pregnancy				
Induced abortion	27.9	12.4	2.7 (induced abortion vs. other outcomes)	1.5, 4.8
Live birth	53.5	71.0		
Stillbirth	1.6	1.0		
Spontaneous abortion	17.1	15.5		
	(n = 129)	(n = 193)		
Previous preterm delivery (last live birth)			23.7 (previous preterm vs. term delivery)	9.3, 60.7
Preterm	42.7	3.0		
Term	57.3	97.0		
	(n = 96)	(n = 164)		

more likely than the controls to have had a diagnosis of placenta previa, abruptions, and incompetent cervix. With regard to urinary tract infections, nine cases (5.1%), as compared to two controls (0.6%), had had a positive test for bacteriuria during the third trimester. All but one had been treated with antibiotics.

Review of the questionnaire as well as the hospital record data also suggested that the cases had slightly higher rates of heart disease and uterine malformations (bicornuate uterus, DES daughter) than did the controls. No differences were found in the distribution of preeclampsia, mild morning sickness, or hyperemesis. When preterm deliveries that resulted from obstetric intervention were included, the cases as compared to the controls had a threefold excess of preeclampsia. Mean hematocrit and hemoglobin values before delivery were only slightly higher for the controls as compared to the cases. Comparisons of the distribution of hematocrit and he-

TABLE 3

Distribution of Cases and Controls by Selected Historical Gynecologic Characteristics and Odds Ratios

Historical gynecologic characteristic	Cases % (n = 175)	Controls % (n = 313)	Odds ratio	95% Confidence intervals
Dilatation and curettage	18.4	11.2	1.8	1.2, 2.4
Surgery, cervix, uterus, or vagina	11.4	5.8	2.1	1.1, 4.1
Infertility	21.1	11.2	2.1	1.3, 3.5

TABLE 4

Occurrence of Selected Pregnancy Complications for Cases and Controls and Tests of Statistical Significance

Complication	Cases (n − 175)	Controls (n = 313)	Statistical test
	No. (%)	No. (%)	
Urinary tract infection			
First trimester	3 (1.7)	8 (2.5)	p = 0.8 (F)
Second trimester	9 (5.1)	5 (1.6)	$\chi_1^2 = 5.06^*$
Third trimester	9 (5.1)	2 (0.6)	$p < 0.01^{**}$ (F)
Spotting or light bleeding			
First trimester	34 (19.4)	36 (11.5)	$\chi_1^2 = 5.74^*$
Second trimester	14 (8.0)	10 (3.2)	$\chi_1^2 = 4.56^*$
Third trimester	15 (8.6)	4 (1.3)	$\chi_1^2 = 14.07^{**}$
Heavy bleeding			
First trimester	3 (1.7)	0 (0.0)	p = 0.10 (F)
Second trimester	8 (4.6)	0 (0.0)	$p < 0.01^{**}$ (F)
Third trimester	8 (4.6)	1 (0.3)	$p < 0.01^{**}$ (F)
Placenta previa (marginal and complete)			
Second trimester	1 (0.6)	0 (0.0)	p = 0.7 (F)
Third trimester	5 (2.8)	1 (0.3)	$p < 0.01^{**}$ (F)
Placental abruption			
Second trimester	2 (1.1)	0 (0.0)	p = 0.26 (F)
Third trimester	12 (6.9)	1 (0.3)	$p < 0.01^{**}$ (F)
Incompetent cervix (second and third trimesters)	14 (8.0)	0 (0.0)	$p < 0.01^{**}$ (F)

F = Fisher's exact test.
* $p < 0.05$.
** $p < 0.01$.

moglobin values also failed to reveal any significant differences between cases and controls.

With regard to diet and weight gain during the pregnancy, a slightly higher proportion of the cases than the controls reported eating "less than usual" during each trimester of pregnancy. The average weight gain for the cases (21.6 lbs.) was also much lower than for the controls (30.8 lbs.). Considering the longer gestational period for the controls, their higher weight gain is to be expected. However, even when a recommended schedule of weight gain was used which adjusted for pregnancy duration (24), the proportion of the cases that had an inadequate weight gain was close to three times as high as it was for the controls (Table 5). The preceding association also held after excluding deliveries resulting in babies with birth weights below the 25th percentile.

Finally, with regard to antepartum care (Table 5), a much higher proportion of the cases than the controls represented clinic as opposed to private patients. The cases also reported seeking prenatal care at a slightly later date than the controls. However, only a marginally lower proportion of cases than controls did not adhere to the schedule recommended by local obstetricians on number of expected prenatal visits by gestational age. Similar results were obtained when the hospital record data were used. Only seven patients (one control and six cases) had not received any antepartum care.

Because many of these apparent risk factors are correlated with each other, multivariable techniques were used to test the effect of each one of the risk factors while holding the effects of the other risk factors constant. The use of these techniques resulted in a considerable reduction in the number of significant risk factors. For instance, the association of age and marital status with preterm delivery was no longer apparent once socioeconomic status was taken into account. Likewise, infertility history explained why histories of dilatation and curettage and gynecologic operations were related to preterm delivery. Also, age at menarche, mean variability of menstrual cycles, and type of antenatal service did not attain statistical significance when tested with several other risk factors simultaneously.

The following variables remained as important determinants of preterm delivery: low socioeconomic class, low pregravid weight, inadequate weight gain during the pregnancy, previous preterm delivery, history of infertility problems, history of induced abortions, vaginal spotting or light bleeding during the first trimester, antepartum hemorrhage and placental abnormalities, third trimester urinary tract infection, and incompetent cervix (Table 6). Second and third trimester vaginal spotting or light bleeding as well as second trimester urinary tract infection had been tested in models with fewer variables and had also been found to be statistically significant. The analysis also indicated that black women were at decreased risk for preterm delivery. Possible reasons for this unexpected finding are discussed below.

Since some of the adjusted odds ratios in Table 6 are based on small numbers, they are probably

TABLE 5

Distribution of Cases and Controls by Adequacy of Weight Gain and Antepartum Care, Tests of Statistical Significance, and Odds Ratios

Characteristic	Cases % (n = 175)	Controls % (n = 313)	Statistical test	Odds ratio	95% Confidence intervals
Weight gain					
Inadequate	29.7	11.5		3.3	2.0, 5.3
Adequate	68.6	86.9	$\chi_1^2 = 24.13^{**}$	(inadequate vs adequate)	
Unknown†	1.7	1.6			
Prenatal care					
Clinic	29.1	16.6		2.1	1.4, 3.3
Private	68.0	83.1	$\chi_1^2 = 10.86^{**}$	(clinic vs. private)	
No care†	2.9	0.3			
No. visits					
Fewer than recommended	13.7	11.5		1.2	0.7, 2.2
Equal or greater than recommended	83.4	86.9	$\chi_1^2 = 0.39$	(inadequate vs. adequate frequency)	
Unknown†	2.9	1.6			
Mean gestational week, first prenatal visit	10.8	10.0	$t_{477} = 1.73$		

** $p < 0.01$.

† Excluded from analysis.

TABLE 6
Adjusted Odds Ratios for Risk Factors Significantly Associated with Preterm Delivery

Risk factors	Adjusted odds ratios*	95% Confidence intervals
Race (black/white)	0.5	0.2, 0.9
Socioeconomic status (class)	5.5[†]	2.1, 14.2
Pregravid weight (pounds)	0.8[‡]	0.7, 0.9
Weight gain (inadequate/adequate)	4.3	2.3, 8.0
Previous preterm delivery (yes/no)	29.8	9.8, 90.4
Infertility history (yes/no)	3.4	1.8, 6.5
History of induced abortion (yes/no)	4.6[§]	2.2, 9.4
First trimester vaginal spotting or light bleeding (yes/no)	2.8	1.4, 5.4
Antepartum hemorrhage and placental abnormalities[‖] (yes/no)	25.9	5.4, 125.3
Third trimester urinary tract infection (yes/no)	6.2	1.2, 31.8
Incompetent cervix (yes/no)	∞[#]	

* Odds ratios obtained from multiple logistic model that tested for effects of the given variables simultaneously, excepting odds ratios for previous preterm delivery, antepartum hemorrhage and placental abnormalities, and third-trimester urinary tract infection; because of small numbers, these odds ratios were obtained from models containing fewer variables.

[†] Class V versus Class 1.

[‡] An increase of 10 pounds.

[§] When pregnancy order was included as a controlling variable, the adjusted odds ratio was reduced to 2.2.

[‖] Combines uterine bleeding, placenta previa, marginal sinus rupture, and placental abruption.

[#] Since no controls were diagnosed as having an incompetent cervix, the odds ratio approaches infinity.

unstable. Nevertheless, they provide some indication of the magnitude of the various risk factors. Accordingly, it appears that a previous preterm delivery, antepartum hemorrhage and placental abnormalities, a third trimester urinary tract infection, and low socioeconomic status represent the strongest risk factors for preterm delivery.

Discussion

Some general limitations of the investigation need to be noted. Although no substantial differences were found when the response data were compared with hospital records recorded prior to the delivery, it is possible that women who delivered a preterm infant were more likely to recall specific exposures than were women who delivered term infants. Interviewer bias can also not be discounted, since the identity of the cases and controls was known at the time of the interviews. However, information was obtained from a standardized, structured interview schedule, and probing was not used to elicit responses. Furthermore, the timing of the deliveries did not always reflect the natural history of premature labor. For example, some patients with premature rupture of the membranes were induced, and a few patients in premature labor were treated with drugs in an attempt to delay delivery. On the other hand, efforts were made to increase the homogeneity of the case group by excluding the preterm deliveries that resulted from obstetric intervention.

The actual evaluation of gestational age may also have influenced some of the results, as has been discussed elsewhere (14). The use of the Dubowitz score precluded the errors associated with recall of menstrual dates. However, comparisons of case-control classifications by the Last Menstrual Period method and the Dubowitz score suggest that the latter method may have overestimated the gestational age of some of the black babies. This possible bias in the Dubowitz score, which may reflect a more rapid maturation of black babies in utero, might explain the discrepancy between the results for race of this study and others (25, 26). At the same time, it could be argued that the Dubowitz method, because it measures indices of maturity, may be a more suitable estimate of preterm delivery than chronological age. Although there is some recent evidence (27) that the Dubowitz score tends to overestimate gestational age for extremely premature infants, it is unlikely that this bias would affect the results of this investigation, because the infants were simply classified as preterm or term. It should also be noted that black women were found to be at a decreased risk of preterm delivery only after controlling for such factors as socioeconomic status which in turn are closely related to race.

With regard to other sociodemographic factors, the literature suggests that young women (26, 28–31), unmarried women (27, 29, 32), and those of low socioeconomic status (25, 28, 29, 33) have an increased risk of preterm delivery. Although the results of the multivariate analysis of the present study indicate that socioeconomic status, as measured by a combined index of education and occupation, appeared to be a more important determinant of preterm delivery than age or marital status, the sample size may not have been sufficient to properly sort out the independent effects of variables that are as closely related as the three preceding ones.

The association between low pregravid weight and preterm delivery has been noted by others

(28) but is still somewhat surprising, as maternal weight would be more logically correlated with birth weight than gestational age. The smaller uterine size of light women may play a role (25). The lack of any consistent association between maternal stature and preterm delivery is in agreement with several previous investigations (28, 29, 31). While low maternal weight gain has been found to be a predictor of preterm delivery in some studies (31, 33), the weight gain result needs to be interpreted with caution. First, weight gain does not distinguish between fluid retention and an increase in body mass. Second, the pattern of weight change over time was not measured. Third, weight gain can at best reflect the quantity but not the quality of food intake. Finally, inadequate weight gain may simply be a consequence of other problems which are themselves directly related to the preterm delivery. Despite these reservations, an insufficient weight gain may be regarded as a warning sign of an impending preterm delivery.

The substantially higher proportion of preterm deliveries among those who had a preceding preterm birth confirms the repetitive nature of such deliveries (30, 32–34). The finding that gravidity was not an important risk factor when tested in the presence of other variables was not unexpected; parity has generally been found to be a weak predictor of preterm delivery (26, 31). As has been discussed previously (14), the association between a previous induced abortion and subsequent preterm delivery is in agreement with a few investigations (35, 36), but not others (37–39). Because of the retrospective design of this study, selective recall among cases and controls is possible, although a check of hospital delivery records showed little underreporting or bias in the recall of abortions.

It has been suggested that if an induced abortion adversely affects subsequent pregnancy outcome, cervical insufficiency or placental dysfunction due to uterine adhesions may be the responsible mechanisms (40). The present study did not confirm any relationship between a prior induced abortion and subsequent placental problems, but women who were diagnosed as having an incompetent cervix were more likely to have had a previous induced abortion than women who did not have cervical incompetence. Given the available evidence (40), particularly for more recently performed abortion procedures, cervical incompetence probably represents a rare sequela of induced abortions.

The multivariate analysis also showed that a history of subfertility or infertility problems rather than exposure to previous gynecologic procedures had an influence on pregnancy duration. Since no information was obtained on the nature of the reproductive problem, it can only be theorized that the cause of the infertility problem might, in some patients, have been responsible for the shortened pregnancy duration. Funderburk (41) has similarly found that subfertile parents have increased proportions of preterm infants.

The findings with regard to pregnancy complications are, in general, consistent with the literature. The occurrence of antepartum hemorrhage (28, 31, 42, 43), abruptions (42, 43), and previas (30, 33, 42, 43) as well as the diagnosis of an incompetent cervix (30, 42) are well-established precursors of premature labor. The increased risk of a preterm delivery after vaginal spotting or light bleeding in early pregnancy may not be as widely recognized, but it has been noted in other patient populations (30, 44, 45). The absence of any association between pre-eclampsia and preterm delivery probably reflects the fact that most of the early deliveries associated with pregnancy hypertension were terminated deliberately by obstetric intervention. Analysis of the Collaborative Perinatal Project data (42) has also shown that pre-eclampsia is associated with intrauterine growth retardation and not premature labor.

The association between symptomatic urinary tract infection and preterm delivery supports the finding originally reported by Kass (46). There is currently considerable interest in the role of infections, particularly those related to sexually transmitted diseases, in the etiology of prematurity (47–49). Although growing evidence implicates genital pathogens in preterm delivery, the nature of the association remains to be clarified (47–49).

Lack of prenatal care has been found to increase the risk at least of low birth weight infants (50, 51). This study as well as others (52, 53), however, provides no convincing evidence that the timing and frequency of prenatal visits per se have an important effect on pregnancy duration. Nevertheless, recent evidence suggests that antenatal care that incorporates preterm prevention strategies may be instrumental in lowering the incidence of preterm deliveries. Specifically, a preliminary report from a preterm birth prevention program in San Francisco (54), which combines early identification of high risk patients with patient education regarding early signs of preterm labor and tocolytic therapy, suggests a substantial reduction in the preterm rate. A collaborative study is currently evaluating whether similar programs will be effective in other population groups.

Although few of the risk factors identified in this report, or those that are used for identifying high risk patients in the aforementioned prevention program (55), are amenable to change, they can at least alert the clinician to the need for closer patient monitoring. The success of such an approach is, of course, ultimately dependent on the early enrollment of high-risk patients in antenatal programs.

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Rubella Susceptibility among Prenatal and Family Planning Clinic Populations

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Abstract

Rubella infections during pregnancy can have devastating results. To assess rubella susceptibility among women who are pregnant or at risk of becoming pregnant, we studied 764 women attending The Mount Sinai Medical Center Family Planning and Prenatal Clinics from December 1982 to April 1983. We found an overall seronegativity rate of 14%. Women who had not been effectively immunized against rubella or had not acquired natural immunity were a significant proportion of our clinic population. These data prompted the expansion of rubella screening and immunization to Family Planning Clinic and In Vitro Fertilization Program patients and hospital personnel dealing with these women.

Women of childbearing age and probable fertility, who are effective contraceptors, and who also are susceptible to rubella are ideal candidates for an immunization program to prevent congenital rubella syndrome. Given the devastating effects on the fetus of rubella infection during pregnancy, a ready means for eliminating the problem, and a target population, we began screening family planning clinic patients to determine the seronegativity rate, both as a measure of the prevalence of congenital rubella syndrome risk and to assess the need for a rubella vaccination program. Prenatal screening and postpartum vaccination programs were already in effect.

In contrast to its relatively mild results in children and adults, the rubella RNA virus can be devastating to a fetus. Congenital rubella syndrome can affect many organ systems, causing deafness, physical and mental growth abnormalities, cardiovascular lesions, hepatosplenomegaly, jaundice, bone lesions, interstitial pneumonitis, thrombocytopenic purpura, central nervous system disorders, immunologic deficiency, other ocular defects including glaucoma and retinopathy, and spontaneous abortion and stillbirth (1).

Rubella vaccine first became available in 1969. Subsequently, New York City school admission requirements included certification that the child either had received rubella vaccine or had demonstrated serologic evidence of rubella antibodies, unless immunization would jeopardize the child's health or violate religious beliefs. By 1980, the rules were amended to require documentation for continued school attendance, not just admission.

However, these requirements have not always been enforced completely. Furthermore, women who entered school before immunization was available or required, also escaped contact with naturally occurring rubella, entered the region after school age, or had ineffective vaccination all contribute to a susceptible pool.

Methods

From December 1982 through April 1983, we tested all women attending the Family Planning

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Clinic and the Prenatal Clinic at The Mount Sinai Medical Center for rubella serology, using the Rubazyme test (Abbott Laboratories, Abbott Park, IL 60064), an enzyme-linked immunosorbent assay for IgG specific to rubella. We recorded results by year of birth.

Our clinic population consists primarily of New York City residents. Over 60% are Hispanic and about 35% are black. About 60% were born in New York City, 20% were born in Puerto Rico, and another 10% were born outside the U.S. About 65% were never married.

TABLE 1

Rubella Seronegativity Rates among Family Planning and Prenatal Clinic Patients by Year of Birth

Year of Birth (Age)	Family Planning No. SN (%)/Total	Prenatal No. SN (%)/Total
<1943 (>40)	1 (6)/16	0 (0)/1
1943–47 (35–39)	3 (9)/33	2 (8)/24
1948–52 (30–34)	11 (15)/71	6 (13)/46
1953–57 (25–29)	17 (14)/121	10 (12)/85
1958–62 (20–24)	22 (13)/174	16 (16)/100
1963–67 (15–19)	2 (10)/20	19 (30)/64
≥1968 (≤14)	0 (0)/1	0 (0)/8

Results

The seronegativity rate for the 436 women tested from the Family Planning Clinic was 13% (95% confidence interval, 9.8%–16.2%). For comparison, 328 women attending the Prenatal Clinic during the same period had a seronegativity rate of 15% (95% confidence interval, 11.1%–18.9%), giving an overall rate of 14% for the total group of 764 (95% confidence interval, 11.5%–16.5%).

The age range was 13–53 (Fig. 1). Comparing the two clinic populations, we found comparable seronegativity rates except for the peak in the Prenatal Clinic population among women born in 1963–1967 (Table 1). To reduce fluctuations from small numbers, we pooled the data from both clinics to calculate age-specific seronegativity rates. These fluctuate between about 10% and 20%, with wider fluctuations at the age ranges for which we had fewer data (Fig. 2).

Discussion

Over the past several years, there has been a generally downward trend in the incidence of reported rubella in the United States (2) and in New York City, which had 104 cases in 1980, 55 in 1981, and 36 in 1982 (3). For the United States, children under 5 years of age (the age that dominates our waiting-room population) had the highest overall incidence rate in 1981, although the age-specific rates increased most for those aged 25–29 (4). This older group is the "baby boom" generation, a cohort that is both numerically larger and expressing its fertility potential later than its predecessor (5). These people were born too soon for routine early childhood immunization with rubella vaccine, which was first licensed in 1969. In addition, they missed the New York City school admission screening and the subsequent documentation required for continued school attendance. Furthermore, thanks to the efficacy of the vaccine in interrupting the characteristic 6–9-year rubella epidemic cycle, these people have had less opportunity to acquire immunity naturally.

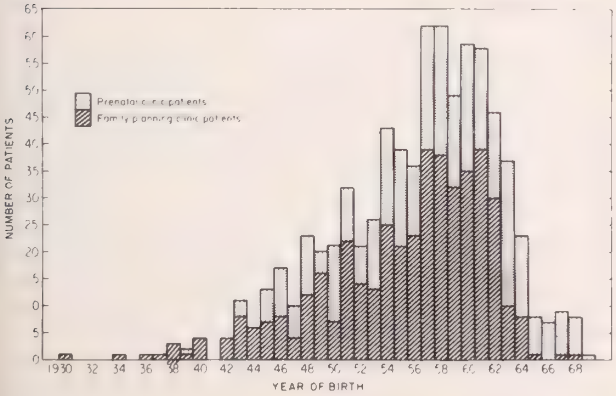

Fig. 1. Numbers of family planning and prenatal clinic patients by year of birth.

Data from the Centers for Disease Control have suggested that the incidence of congenital rubella has declined, although reporting has been poor (2, 6, 7). In addition to incomplete reporting, the accuracy of diagnosis cannot always be verified for reported cases. Because most cases are reported within the first year of birth, those with more subtle or later manifestations (such as hearing deficits) are probably uncounted.

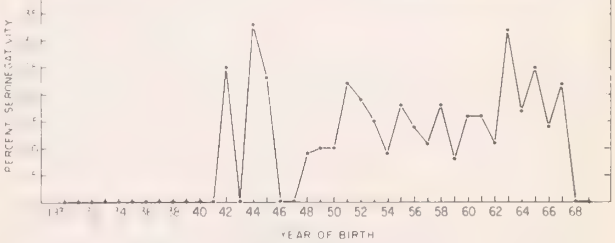

Fig. 2. Percent of seronegative patients by year of birth in combined family planning and prenatal clinic populations.

The 10%–20% rubella susceptibility of our population is comparable to the susceptibility prevailing before the vaccine was available and similar to that of other groups of young adults in the United States, including cadets at the US Merchant Marine Academy, California women undergoing either prenatal or premarital screening, and clients of family planning clinics in Philadelphia (2, 4, 6–8). The persistence of this 10%–20% seronegativity rate among adolescents and young adults is consistent with the continuing outbreaks that have been observed in this population (2).

Recent outbreaks of rubella in New York City and Chicago and in medical facilities, including those serving pregnant women, are cause for concern. In 1983, at least 86 cases of rubella occurred among workers at a bank in Manhattan, 3 cases occurring among pregnant women (9). After a 1978 rubella outbreak in Chicago, an intensive survey identified 31 infants with congenital rubella syndrome (10). Rubella outbreaks (11–16) among hospital personnel, including male obstetrics house staff and a nonpregnant female obstetrics nurse, have been compared to the "Trojan horse that surreptitiously introduces an army of rubella viruses into prenatal clinics and hospitals caring for obstetric patients" (16).

These outbreaks could have been prevented by rubella vaccination, which can be obtained for less than $5 per dose. The current vaccine, RA 27/3, available since 1979, is a live attenuated rubella virus vaccine produced in human diploid cell cultures. It has an efficacy greater than 97% and persists for at least 10 years, if not for life (17–19). Although reinfection may be more likely to occur after vaccination than after naturally acquired immunity, it is usually subclinical and is accompanied by an antibody response indicative of immunologic recall (20). Reports of women with demonstrable antibody titers giving birth to infants with congenital rubella syndrome are extremely rare and somewhat doubtful (21–23).

The risks of rubella vaccination are minimal (4). Vaccine reactions are generally mild and less frequent with the newer vaccine, consisting of transient rubella-like symptoms. Up to 40% of vaccinees have had joint pain, but frank arthritis has been rare. Arthralgia and transient arthritis occur more frequently and tend to be more severe in susceptible women than in susceptible children.

Concern about the potential adverse effects of rubella vaccine on a fetus should not deter immunization of women of childbearing age. Close scrutiny by the Centers for Disease Control and others failed to reveal congenital rubella syndrome in a prospective study of the offspring of over 1,000 women who received rubella vaccine either within three months before or three months after their presumed dates of conception (23). Because vaccine viruses can cross the placenta and infect the fetus, the actual risk may not be zero. Thus, because of the theoretical, albeit small, risks to the fetus, immunization should be avoided during pregnancy and for three months prior to conception. However, the vaccine virus is not transmitted to household contacts (22). Therefore, immunization need not be withheld from those with pregnant relatives or friends. Although vaccine virus may be excreted in mother's milk, and seroconversion may occur in breast-fed infants, there is no contraindication to vaccination during breast-feeding (24).

The goal of rubella vaccination programs is to eliminate congenital rubella syndrome, each case of which is associated with an estimated lifetime expenditure of over $220,000 (25). This estimate does not begin to measure the cost in spontaneous and induced fetal deaths, prenatal parental anxiety, and human misery for these individuals, their families, and their communities. Although new cases of congenital rubella syndrome are relatively rare, the potential for their creation exists with current seronegativity rates among fecund women. Pediatric and school health programs could eliminate congenital rubella syndrome within 30 years if total compliance were achieved. However, this slow process could be hastened by the additional targeting of fecund women and those to whom they are exposed. Given the estimates mentioned above, over 44,000 vaccines could be purchased for less than the cost of caring for one case. Distributing the vaccine over 30 years would permit over 1,400 vaccinations per year, enough to cover the entire clientele of this Family Planning Clinic plus the staff with whom they come in contact.

One strategy is to screen first, and then vaccinate only those who are found to be seronegative and presumed to be susceptible. Drawbacks to this strategy include the risk of false negative or false positive serology tests (26), loss to follow-up (with potential interval pregnancies) of seronegative women who do not return for vaccination, and the costs of the screening program itself (both in personnel time and laboratory supplies).

An alternative is to vaccinate everyone except those who have proof of immunity (seropositivity or prior vaccination) or who have proven contraindications to rubella vaccine, such as pregnancy, febrile illness, allergies, or altered immune status. Objections to this strategy include the costs of personnel and materiel and the discomfort involved in unnecessarily vaccinating seropositive individuals, each of whom must first give consent.

The pros and cons for alternate strategies and target populations have been discussed (2, 4, 9, 12–16, 25, 27–37). Although so-called herd immunity guards against major outbreaks, it does not prevent "minor" ones, the results of which can be quite disruptive and devastating. Vaccinating postpubescent males and females in population groups such as college students, office workers, and military recruits protects these individuals against rubella and reduces the chance of epidemics among these partially immune groups. To eliminate the Trojan horse phenomenon, all health care personnel in contact with susceptible fecund women must also be involved—including men as well as women, volunteers as well as employees, clerical as well as medical staff, students, observers—and uncooperative physicians.

The strategy chosen to eliminate congenital rubella syndrome will depend upon the organization, resources, relative costs, risks, and recall ability of the individual institution or community. The estimated 1981 national benefit/cost ratio was over 11:1 (25). The favorable benefit/cost ratio, both in human and in financial terms, makes rubella vaccination programs well worth the effort.

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Tuberculosis Chemoprophylaxis for Diabetics: Are the Benefits of Isoniazid Worth the Risk?

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Abstract

The American Thoracic Society has recommended isoniazid chemoprophylaxis for tuberculin-positive but asymptomatic, chest x-ray negative, adult diabetics. This is despite little evidence that diabetics are at increased risk for active tuberculosis. Furthermore both the diabetes and tuberculosis mortality rates are declining and isoniazid therapy is not totally effective and carries risks of morbidity and death. We performed a decision analysis comparing chemoprophylaxis and no chemoprophylaxis, using isoniazid-hepatitis risks, Markov-process determined life expectancies, and tuberculosis risks. We reviewed the literature to obtain isoniazid-hepatitis morbidity and mortality rates, isoniazid effectiveness, tuberculosis activation and case-fatality rates, and diabetes mortality rates.

Although the results show isoniazid chemoprophylaxis to be beneficial in almost all age, sex, and race cohorts, the benefits are small and measured in days. Combining all assumptions favoring chemoprophylaxis, life expectancy for 50-year-old white men, for example, is extended by 39 days (an increase of 0.7%). Combining all assumptions favoring the strategy of no chemoprophylaxis for the same cohort, life expectancy is the same for both strategies. Thus the isoniazid strategy for asymptomatic adult diabetics has a small effect. We suggest that the recommendations be qualified to encourage a joint decision by patient and physician.

For almost twenty years the American Thoracic Society and the Centers for Disease Control have recommended isoniazid chemoprophylaxis for asymptomatic people with positive tuberculin skin tests who are at high risk for developing active tuberculous disease: household contacts (even if tuberculin-negative) of people with active tuberculosis; recent tuberculin converters; people with inactive tuberculosis inadequately treated in the past; people with abnormal chest x-rays; reactors under the age of 35; and reactors in "special clinical situations." Included in this last group are people undergoing corticosteroid or immunosuppressive therapy or with gastrectomy, Hodgkin's disease, silicosis, or "instability of severe diabetes" (1).

The recommendation for chemoprophylaxis of tuberculin-positive diabetic patients was presumably based on reports concerning the association between tuberculosis and diabetes (2, 3) and on evidence that tuberculosis was diagnosed more frequently in people with severe or out-of-control diabetes than in people with mild or controlled diabetes (2). Despite these early reports, little confirmatory evidence has documented an increased tuberculosis risk among diabetics. Some authorities do not even consider diabetes a risk factor for active tuberculosis (4).

Shortly after the initial recommendation, it became evident that mild liver dysfunction occurred in 10%–20% of people taking isoniazid and that some developed clinical, at times fatal, hepatitis (5). Despite this, the recommendation for chemoprophylaxis in diabetics with positive skin tests has not been reexamined; furthermore, the rec-

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ommendation is no longer limited to those with severe or unstable disease (6).

This question is especially salient today because of the declining mortality rate for those with diabetes (7) and the declining incidence and mortality rates of tuberculosis, in both the diabetic and general population (8–10). We therefore studied the relative risks and benefits of chemoprophylaxis among diabetics. The question addressed is: Do the benefits of chemoprophylaxis outweigh the risks?

Methods

We performed a decision analysis (11) using published data to determine the relative life expectancies of patients who take or refuse chemoprophylaxis. The analysis requires the representation of clinical strategies by a decision tree, the assignment of probabilities for the occurrence of events, the calculation of life expectancies so that the clinical strategies can be compared, and a sensitivity analysis which tests whether the decision depends on reasonable variations in probabilities.

The Decision Tree

The decision tree (Fig.) poses a choice between two strategies for asymptomatic, tuberculin-positive diabetics: one year of isoniazid chemoprophylaxis, and no chemoprophylaxis. The patients for whom this model applies have diabetes, are age 35 or older, have positive tuberculin skin tests, and no evidence of active tuberculosis or fibrotic lesions on chest x-ray. The model does not apply if there is another indication for chemoprophylaxis.

If a person chooses isoniazid chemoprophylaxis, three alternative events can occur. First, isoniazid therapy for a year without complications. Second, isoniazid therapy accompanied by development of nonfatal hepatitis. It is assumed that if this occurs, the drug will be stopped, but that the person has partial protection equivalent to having taken the drug for 12 weeks (62% of those who develop hepatitis do so within 12 weeks of starting therapy) (12). Third, isoniazid therapy accompanied by development of fatal hepatitis. It is assumed that these persons die in the twelfth week (12).

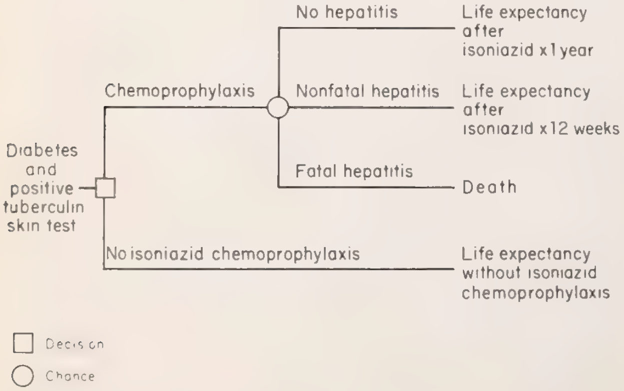
No hepatitis
Life expectancy after isoniazid x1 year
Chemoprophylaxis
Nonfatal hepatitis
Life expectancy after isoniazid x12 weeks
Diabetes and positive tuberculin skin test
Fatal hepatitis
Death
No isoniazid chemoprophylaxis
Life expectancy without isoniazid chemoprophylaxis
☐ Decision
○ Chance

Figure. Decision tree illustrating consequences of choice between taking and not taking isoniazid.

If a diabetic chooses not to take isoniazid, tuberculosis activation remains a risk. Of course the isoniazid-takers are also at such risk, lowered by either the one-year or the 12-week effectiveness of the drug. The risks of isoniazid hepatitis are assumed to occur only during the initial year of therapy. The risk of tuberculosis activation is assumed to be lifelong.

The outcome of our analysis is life expectancy. We calculated life expectancy with a Markov process utilizing yearly probabilities of developing active tuberculosis, dying from active tuberculosis, and dying from all other causes. These transitional probabilities are computed for various age, sex, and race cohorts to provide a summary statistic (life expectancy) for analysis.

Probability Values

The following probability values are necessary for the analysis: the risk of developing isoniazid hepatitis; the risk of dying from isoniazid hepatitis; the effectiveness of isoniazid chemoprophylaxis; the annual mortality rate of diabetics; the annual probability of developing active tuberculosis; and the tuberculosis case-fatality rate. Tuberculosis activation rates (r) were converted (13) to annual probabilities (P) by the formula $P = 1 - e^{-r}$. Where published rates are controversial, we varied the rates over reasonable ranges.

Isoniazid-hepatitis risks were taken from the Cooperative Surveillance Study conducted by the U.S. Public Health Service among 13,838 people in 21 health departments (12). Ninety-two probable and 82 possible cases of isoniazid-related hepatitis occurred. Case rates varied with age: for the combined probable and possible cases, the rates per 1,000 persons were 23 for those 35 to 49 years, 41 for those 50 to 64 years, and 26 for persons 65 years and older. We assumed the rates are similar among all races and both sexes. Among all 13,838 participants, the isoniazid-related case fatality rate was 57.8 per 100,000 persons and was assumed to be constant regardless of age, sex, and race. In the sensitivity analysis the hepatitis rate and the case-fatality rate were varied from 75% to 125% of the base values.

The benefits of isoniazid chemoprophylaxis were detailed by Ferebee in a comprehensive review (14). The U.S. Public Health Service conducted a large-scale study among people in mental institutions considered to have longstanding infections (not recent converters or contacts of people with active disease). They found that one year of isoniazid was 70% effective in preventing activation among those with negative chest x-rays. More recently, the International Union Against Tuberculosis reported the results of a large five-year trial of people with fibrotic lesions on x-ray. They found a 75% reduction in activation from isoniazid (15). We used 70% for our best estimate, and varied the effectiveness from 60% to 80% in the sensitivity analysis. For those diabetics who develop nonfatal hepatitis and therefore stop the drug (at an average of 12 weeks), the best available evidence demonstrates a 16% reduction in reactivation (14). This was varied from 12% to 20% in the sensitivity analysis.

Annual tuberculosis activation rates for nondiabetics were taken from Comstock and Edwards, who estimated rates dependent on age, race, and sex up to age 65 by combining several observational studies and chemoprophylaxis trials. The rates varied between 35 and 130 cases per 100,000 tuberculin reactors (16). We estimated activation rates for elderly nondiabetics by averaging the low figures found by Grzybowski and Allen in their Toronto survey (17) with the higher rates calculated by Stead and Lofgren in their Arkansas survey (18).

The overall case-fatality rate for tuberculosis was 9.3% in 1978 (19). Because the Centers for Disease Control do not report tuberculosis mortality data by age, sex, and race, we calculated these rates by combining case rates and fatality rates published in U.S. vital statistics (19, 20). In the sensitivity analysis, we varied these figures from 75% to 125% of the base rate.

The risk of tuberculosis in past years was considered greater among diabetics than among nondiabetics. It is difficult to tell whether this is because activation occurred more frequently, the disease lasted longer, or mortality was higher. A 1949 Philadelphia survey found the prevalence of tuberculosis to be twice that of a nondiabetic population (21), and a 1954 Swedish survey found a fourfold greater prevalence among diabetics (2). A 1930–1956 cohort study of mortality among 21,477 diabetic patients at the Joslin Clinic found 21 deaths from tuberculosis—1.5 times the expected number (7). The Joslin Clinic study did not indicate whether the higher mortality occurred because tuberculosis activated more frequently among diabetics, or because the tuberculosis case-fatality rate was higher among diabetics. The Philadelphia and Swedish surveys suggest the former, although a combination of the two factors may be the case.

We used an annual probability of activation 1.5 times the nondiabetic rate and the same case-fatality as in the nondiabetic population. In the sensitivity analysis we varied the activation rate from one to four times the rate for the nondiabetic population. We also tested whether the risk for diabetics was from high tuberculosis case-fatality rates rather than from high tuberculosis activation rates.

Diabetic mortality data was taken from the Statistical Bureau of the Metropolitan Life Insurance Company (22), which derived life expectancies from the National Health Interview Survey and from mortality data from statewide studies in Iowa and Pennsylvania (23, 24). We assumed the annual mortality rate is an inverse function of life expectancy (25) and that the rates between races are the same (10). Because of underreporting, these estimated rates are probably lower than reality (24). Therefore, in the sensitivity analysis, we varied the mortality rate to correct for these low estimates: since it has been estimated that between 7.6% and 22.8% of death certificates do not report diabetes, we performed the analysis using life expectancies adjusted for 20% underreporting (26).

Calculations of Life Expectancy

Life expectancy was calculated by the Markov-cohort method (27, 28) using annual probabilities of diabetes mortality, tuberculosis activation, and tuberculosis case-fatality. For the people who choose isoniazid chemoprophylaxis, the probability of tuberculosis activation was accordingly decreased. The life expectancies were then placed in the decision tree.

Calculations were performed on a Cromemco CS1 microcomputer using the C language. We performed a sensitivity analysis with 5% per year discount rate. Discounting is a method used by policy analysts and economists to diminish future benefits and risks relative to present-day benefits and risks (11). The 5% rate is widely accepted.

Results

Average Life Expectancy

Table 1 shows the expected gains in average life expectancy from chemoprophylaxis by age, sex, and race. For all cohorts the benefits of iso-

TABLE 1

Life Expectancy with and without Isoniazid Chemoprophylaxis and Marginal Benefit of Chemoprophylaxis

	Life Expectancy for Cohort (years)		
	Age		
	35	50	65
Nonwhite men			
with isoniazid	22.045	15.798	10.183
without isoniazid	22.035	15.786	10.173
difference	0.010	0.012	0.009*
White men			
with isoniazid	22.042	15.793	10.176
without isoniazid	22.023	15.770	10.151
difference	0.018*	0.023	0.025
Nonwhite women			
with isoniazid	24.994	18.566	12.717
without isoniazid	24.981	18.551	12.702
difference	0.013	0.015	0.014*
White women			
with isoniazid	24.991	18.558	12.707
without isoniazid	24.970	18.525	12.671
difference	0.021	0.032*	0.036

* Difference due to rounding.

TABLE 2

Sensitivity Analysis for Life Expectancy with and without Isoniazid Chemoprophylaxis and Marginal Benefit of Chemoprophylaxis

	Life expectancy for 50-year-old white men		
	With isoniazid Years	Without isoniazid Years	Difference (isoniazid benefit) Years (Days)
Best Estimate	15.793	15.770	0.023 (8)
Combination of probabilities favoring chemoprophylaxis	15.774	15.667	0.107 (39)
Combination of probabilities favoring no chemoprophylaxis	11.861	11.861	0
Discounting 5% per year, best estimate	10.524	10.518	0.007* (2)
High tuberculosis case-fatality rate, low tuberculosis activation rate	15.777	15.720	0.056* (21)

* Difference due to rounding.

niazid chemoprophylaxis outweigh the risks. The cohort that receives the greatest benefit from chemoprophylaxis is 65-year-old white women; they can expect to live 13 days longer, an extension of 0.28% in life expectancy. The cohort that receives the least benefit from chemoprophylaxis is 65-year-old black men; they can expect to live 3 days longer. A cohort of 50-year-old, tuberculin-positive, diabetic white men taking isoniazid chemoprophylaxis have increased life expectancy because of less risk from tuberculosis, but the benefit is diminished by the risk from isoniazid hepatitis; they can expect to live 8 days longer because of chemoprophylaxis.

In a sensitivity analysis, we combined all probabilities that favor chemoprophylaxis of tuberculin-positive diabetics (Table 2): 80% effectiveness of isoniazid, tuberculosis activation rates four times the rate for nondiabetics, 125% of the best-estimate tuberculosis case-fatality rate, and the lowest annual diabetic general mortality rate. Chemoprophylaxis confers an addition to life expectancy of 39 days for 50-year-old white men. This implies an extension of life expectancy of 0.7%. Conversely, we combined all probabilities that favor no chemoprophylaxis: 60% effectiveness of isoniazid; the same risk of tuberculosis activation as nondiabetics; 75% of the best-estimate tuberculosis case-fatality rate; and the highest annual diabetic general mortality rate calculated from 20% underreporting. For 50-year-old white men, life expectancy is the same for either strategy.

Discounting by 5% per year diminished but did not eradicate the benefits of isoniazid: 50-year-old white men live 2 days longer with chemoprophylaxis.

To clarify whether the risk for tuberculin-positive diabetics is from high tuberculosis case-fatality, rather than from high activation rates, we tested tuberculosis case-fatality rates four times those of the general population, while using the nondiabetic population tuberculosis-activation rates. The decision is unchanged: 50-year-old white men live 21 days longer after taking chemoprophylaxis.

Morbidity from Hepatitis and Tuberculosis

Comparisons of morbidity from two different diseases are problematic. Nevertheless, many have compared active tuberculosis and clinical isoniazid hepatitis in order to analyze prevention policies (15, 16, 29); we summarize expected duration of illness from both diseases (Table 3).

Discussion

Decision analysis shows that the benefits of isoniazid chemoprophylaxis outweigh its risks for almost all age, sex, and race cohorts, and that both the benefits and risks are small. Life expectancy is likely to increase by one week. Overall morbidity is unchanged. Many would consider a choice between two competing strategies offering

TABLE 3
Expected Duration of Illness from Active Tuberculosis and Isoniazid Hepatitis

	Without isoniazid chemoprophylaxis Years (days)	With isoniazid chemoprophylaxis Years (days)
35-year-old white men		
Active tuberculosis	0.037 (14)	0.012 (4)
Isoniazid hepatitis	0	0.022 (8)
Total illness	0.037 (14)	0.034 (12)
50-year-old white men		
Active tuberculosis	0.034 (13)	0.011 (4)
Isoniazid hepatitis	0	0.040 (15)
Total illness	0.034 (13)	0.052* (19)
65-year-old white men		
Active tuberculosis	0.031 (11)	0.010 (4)
Isoniazid hepatitis	0	0.025 (9)
Total illness	0.031 (11)	0.035 (13)

* Difference due to rounding.

such small differences in risks and benefits a "toss-up" (30). This analysis illustrates that the choice is not clear-cut.

Our study has several limitations. The repetitive calculations inherent in the process may inaccurately predict life expectancies (27). However, since the purpose of our using this method is to compare average life expectancies among competing strategies, and not to predict life expectancies themselves, we believe that this is a useful construct.

Second, there are uncertainties in the data. All policy analyses should be done with the best available data. Unfortunately the best information may be inaccurate or imprecise. Our estimates of tuberculosis case-fatality rates were derived from aggregated data from vital statistics of case rates and cause-specific death rates. The studies showing the risk of tuberculosis activation between diabetic and nondiabetic groups were often calculated using historical controls (7). We assume these studies were accurate and are still appropriate. Life expectancy for diabetics is, however, increasing (7), and the tuberculosis case-fatality rate is decreasing (9). Therefore our projected figures may not reflect the future risk of tuberculosis for today's diabetics.

Despite these flaws, we believe that our approach deserves consideration, for it subjects a policy statement to a rigorous, explicit analysis. To the best of our knowledge such analysis was not undertaken for the original recommendations. We believe the benefits of isoniazid chemoprophylaxis minimally outweigh the risks for asymptomatic, tuberculin-positive diabetics. Clinicians should be aware that the choice between these two strategies is a "toss-up." Furthermore, there are many uncertainties in the available data which affect the decision. The decision should be one between physician and patient, with necessary consideration of individual risk factors, likelihood of compliance, cost, and appreciation of the difference between a strategy that entails immediate risk with future benefit (the choice of isoniazid chemoprophylaxis) and a strategy that entails immediate benefit with future risk (no chemoprophylaxis).

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Some Effects of a Hospital Employee Strike on Patient Satisfaction

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Abstract

A 55-item questionnaire was administered via telephone to patients prior to (N = 644) and during (N = 906) a strike by hospital employees in order to assess levels of satisfaction with hospital services. Both samples were similar with respect to age, sex, median length of stay, path of admission, and hospital location. Results show that satisfaction levels during the strike were equal to or higher than those obtained pre-strike for most items. Exceptions were in the area of housekeeping and dietary/food delivery. Medical and nursing care scores were higher during than prior to the strike. Scores during the strike period were obtained for early, middle, and late periods. Late strike results tended to be lower than those for earlier period. Implications of the data are discussed.

This paper compares patients' perceptions of hospital services received at The Mount Sinai Hospital, New York City, at two points in time: during the course of a strike by hospital employees and during a period preceding the strike. As such, it examines two important social phenomena, namely, patients' evaluations of the quality of services received from a broad range of providers and departments, and the effect on these subjective quality assessments of a major change in the environment brought about by a labor crisis.

In the last several years, a body of literature has emerged which amply demonstrates a strong association between patients' perceptions and evaluations of their health care and their subsequent health-related behavior (1). Patient satisfaction, for example, has been shown to exert influence over commitment to the therapeutic relationship (2), "doctor-shopping" (3), and decisions regarding maintenance of enrollment in a prepaid group practice (4). Moreover, a number of studies of patients' evaluations of their medical care provides evidence that patients are at least as concerned with the manner in which their social and emotional needs are met as they are with the technical competence of their caregivers (5–8). For hospitalized patients, these data alert us to the significance of interpersonal and environmental processes by which such patients feel comforted, protected, and reassured of continuous personal service. In short, patients' subjective evaluations of health care services bear a significant relationship to their sense of wellbeing. Patient satisfaction, therefore, can be used as a measure of quality of care (9).

Providers of health care services in hospitals, clinicians and managers, need to be alert to situations which pose a threat to patients' sense of wellbeing. Events which undermine feelings of security, or which add discomfort to patients already burdened by the personal crisis of illness can have an adverse effect on patients' abilities to participate in and respond to the therapeutic process. A labor crisis in which a large proportion of hospital employees decide to walk off their jobs is one such threatening event (10). It is surprising, therefore, that the literature reports so few studies of how strikes of hospital employees affect the patients' experience. While analyses of hospital strikes have appeared (11–12), few are based on empirical research.

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The Strike

Members of District 1199 of Retail, Wholesale, and Department Store Employees AFL-CIO struck The League of Voluntary Hospitals and Homes of New York, of which The Mount Sinai Hospital is a member, for a period of 47 days during July and August 1984. At Mount Sinai the 2,900 employees who are 1199 members fall into four functional categories: technical (imaging, laboratory, nursing assistants, etc.), clerical (admitting registrars, unit clerks, accounting clerks, etc.), service (food, housekeeping, escort, laundry, etc.), and maintenance (engineers, repairmen, etc.).

Over the period of the strike, Mount Sinai Hospital in-patient admissions were about 6% below normal levels. The average length of stay for patients admitted during the period declined by approximately 3% and the occupancy rate declined by almost 5%. While walk-in emergency services continued to be provided to members of the community who needed them, most ambulatory care clinics did not operate, or did so at a sharply reduced pace. Essential in-patient care services normally provided by 1199 members were carried out by non-bargaining-unit staff from the hospital and medical school, attending physicians and medical school faculty, and volunteers from the community.

In deciding to mount a survey of patient opinion during the strike, the institution was attempting to provide itself with basic information about the quality of services during a staffing crisis and the effectiveness of plans to maintain adequate levels of quality made in preparation for the emergency.

Methods

Survey Questionnnaire. The development of the questionnaire, a 55-item instrument which is administered over the telephone to patients within 7 days of discharge, has been described elsewhere (13). The content was arrived at through a collaborative process by hospital managers responsible for the services included in the survey and a team of behavioral scientists. The instrument was pretested and revised accordingly. At Mount Sinai, patient satisfaction surveys are conducted three times each year by a team of nonemployee interviewers who are trained by one of the authors. Customarily, data are reviewed by an interdisciplinary committee as a means of initiating corrective action where necessary.

Patients are asked to rate hospital services on a scale in which excellent equals 4, good equals 3, fair equals 2, and poor equals 1. Hospital services rated include: admitting, business office, housekeeping, dietary and food service delivery, escort, x-ray, blood drawing, medical care, nursing care, social work, and hospital in general. Additional information collected includes the subject's path of admission (through the admitting office, the Emergency Room, or direct admission to room), subject's age, sex, length of stay, and room assignment(s). The questionnaire was designed to allow subjects to rate services according to the quality of (a) information provided, (b) promptness of service, (c) caring and courtesy shown by staff members, and (d) environmental aspects (for example, cleanliness of room, tastiness of food, appearance of staff members).

To date, reliability and validity measures have not been calculated, although through factor analysis it has been determined that the 55 items comprise 16 factors. The most clearly defined factors are medical care, nursing care, x-ray services, and operating room escort services.

Population and Sampling Technique. Both samples were selected from discharge sheets kept in the Department of Patient Accounts, excluding psychiatric patients, those admitted to strictly clinical research floors or units, mothers of babies in the neonatal intensive care unit, patients discharged within three days of admission, and patients who live outside of the New York metropolitan area. Subjects who cannot be reached after calling three times are considered nonrespondents. Interviews are conducted in both English and Spanish.

The prestrike sample consisted of a random sample of 1,000 eligible patients discharged between mid May and mid June 1984. Of these, 644 were successfully interviewed, all within 7 days of discharge date. The reasons for nonresponse are as follows: (a) no contact after three tries, 33%; (b) no phone, 19%; (c) refused, 10%; (d) wrong number, 9%; (e) out of New York metropolitan area, 6%; (f) readmitted to hospital, 5%; (g) language, 3%; (h) other, 11%.

The strike sample was a random sample of 1,237 eligible patients admitted and discharged during the strike. Of these, 906 were successfully interviewed, 65% within seven days. Sampling was done on a daily basis during the first two weeks of the survey and on alternate days thereafter to accommodate the demands placed on survey team resources by the unexpectedly lengthy strike.

Of the 331 patients who were not successfully interviewed, the reasons for loss (in rank order) are: (a) no contact after three tries, 35%; (b) no telephone, 16%; (c) patient or family refused interview, 12%; (d) wrong number, 8%; (e) patient readmitted, 7%; (f) out of New York metropolitan area, 5%; (g) unable to get phone number from the chart, 4%; (h) language barrier (other than Spanish), 2%; and (i) "other," including death, out of town, too sick to be interviewed, etc., 11%.

The characteristics of the two samples differ in mean length of stay; the prestrike group is significantly higher (Table 1). Median length of stay, however, is similar for both groups. Location of room, age, sex, and path of admission are not significantly different when the two groups are compared.

TABLE 1

Patient Satisfaction Survey: Comparison of Prestrike (N = 644) and Strike (N = 906) Samples

	Prestrike	Strike
Sex		
Male	39%	41%
Female	61%	59%
Age (years)		
Mean	46.9	45.8
S.D.	22.9	22.3
Path of admission		
Admission Office	67	67
Direct to room	15	15
Emergency room	18	18
Length of stay (days)		
Mean	10	7
S.D.	12.6	5.2
Median	5.7	5.2
Location (pavilion)		
Medical	21%	18%
Private	23%	22%
Maternal-child	33%	36%
Surgical	23%	24%

Results

Scoring excellent as 4, good as 3, fair as 2, and poor as 1, the mean scores for items included in both surveys (Table 2) show 26 of 55 items differing significantly across surveys. Seventeen items were rated significantly higher during the strike than prestrike. Nine items were scored significantly lower for the strike than for the prestrike period.

Of the 17 items with higher strike than prestrike ratings, 14 pertained to medical and nursing care. In fact, every item related to these two services was rated significantly higher by the strike sample. Items rated significantly lower by the strike sample than by the prestrike sample clustered in two service areas: housekeeping, and dietary/food service delivery. Except for items concerned with interpersonal aspects of these services (courtesy and guidance), all items were perceived more negatively by the strike sample than by the prestrike sample. No items related to blood drawing, x-ray, or escort were perceived significantly differently. The item which asks subjects to provide an overall rating for hospital services received was rated significantly higher by the strike sample.

Table 3 reflects the extent to which the prestrike–strike differences held in various hospital locations. In the aggregate, medical care items were rated more highly by subjects receiving care during the strike regardless of location. Nursing care items, however, were rated more highly during the strike period by subjects who received care only in surgical areas and on the semiprivate, medical teaching service. No differences in nursing care items were observed for subjects who received care on units dedicated to maternal-child health, or on the private service. Housekeeping items were rated less favorably during the strike period in all locations except the semiprivate, medical teaching service. This same location was also unique in responses evoked to items relating to food delivery.

In comparing patient ratings of hospital services for different time periods—early, middle, and late—during the strike (Table 2), an analysis of variance showed that changes over time occurred in the following service categories: admitting, business office, medical care, nursing care, and escort.

The net effect of the differences is that in a number of service categories, late strike ratings fell well below those obtained in the first weeks of the labor crisis. The pattern of change varies. One variation, seen in the admitting service, shows a substantial decline in mean scores from the early to the middle period, followed by a slight trend upward at the late period. Another variation, seen in some medical care and nursing care items, is a rise in mean scores between the early and middle periods, followed by a decline in the late period.

With few exceptions, the medical care and nursing care items remain substantially higher in the late strike period than in the prestrike period. For nursing care, this is the case even though large differences in mean scores are noted between early-strike and late-strike items. In other words, for the duration of the labor crisis, patient perception of key clinical services was more favorable than that reported by a similar group of patients just prior to the strike.

TABLE 2

Patient Satisfaction Survey: Mean Scores, All Services Prestrike (N = 644) vs. Strike (N = 906) and Early (N = 402), Middle (N = 282), Late (N = 222) Strike

			Strike		
Prestrike	Strike	Service Item	Early	Middle	Late
		Admitting			
3.27	3.37**	courtesy	3.46	3.29	3.35**
3.17	3.20	promptness	3.24	3.12	3.17
3.24	3.31	response to questions	3.39	3.24	3.28**
3.29	3.33	courtesy (lab)	3.47	3.23	3.23***
		Business office			
2.94	3.10*	response to questions	3.14	3.15	2.99*
3.11	3.18	courtesy	3.16	3.26	3.13
		Housekeeping			
3.07	2.95**	room on arrival	3.00	2.88	2.94
2.96	2.67***	daily cleaning	2.66	2.70	2.61
3.02	2.79***	public areas	2.48	2.51	2.43
2.81	2.49***	bathrooms	2.83	2.77	2.78
3.26	3.19*	courtesy	3.27	3.15	3.12
		Blood drawing			
3.26	3.31	courtesy	3.37	3.30	3.23
3.34	3.31	appearance	3.36	3.30	3.22
3.26	3.23	technique	3.29	3.19	3.15
		Food and beverages			
2.72	2.39***	temperature (hot)	2.37	2.38	2.43
2.81	2.77	temperature (cold)	2.76	2.76	2.72
2.35	2.08***	tastiness	2.05	2.13	2.04
3.03	2.90***	promptness	2.99	2.87	2.78
3.19	3.12	guidance	3.09	3.14	3.14
3.12	3.17	courtesy	3.28	3.14	3.05
		Medical care			
3.47	3.66***	care and concern	3.66	3.70	3.65
3.43	3.60***	explanation (dx)	3.57	3.67	3.60
3.38	3.56***	explanation (tx)	3.52	3.64	3.55*
3.38	3.61***	response to questions	3.60	3.64	3.63
3.43	3.60***	respect of privacy	3.57	3.64	3.64
3.42	3.54***	MD introduction	3.50	3.62	3.56
3.34	3.50***	MD listening	3.48	3.56	3.46
		Nursing care			
3.14	3.23*	information (routine)	3.28	3.25	3.15
3.03	3.15*	explanation (primary nursing)	3.16	3.22	3.09
3.25	3.47***	attitude	3.48	3.54	3.36**
3.14	3.38***	promptness	3.38	3.50	3.22***
2.23	2.47***	willing to help	3.51	3.53	3.34***
3.16	3.29**	instructions (home care)	3.26	3.37	3.25
3.33	3.53***	overall satisfaction	3.54	3.57	3.47
		Social work care			
3.32	3.43	helpfulness	3.44	3.45	3.44
		Escort (Admitting)			
3.15	3.18	promptness	3.26	3.18	3.06**
3.28	3.27	comfort	3.33	3.24	3.22
3.33	3.39	courtesy	3.46	3.28	3.37***
		Escort (OR/recovery)			
3.29	3.36	promptness	3.36	3.39	3.21
3.36	3.39	comfort	3.45	3.39	3.27
3.46	3.50	courtesy	3.56	3.49	3.38
		Escort (x-ray)			
3.08	3.08	promptness	3.13	3.20	2.89
3.21	3.28	comfort	3.26	3.27	3.28
3.31	3.37	courtesy	3.36	3.37	3.40
		Escort (other)			
3.16	3.15	promptness	3.14	3.12	3.14
3.28	3.26	comfort	3.28	3.22	3.17*
3.32	3.35	courtesy	3.39	3.34	3.23

TABLE 2—*Continued*

			Strike		
Prestrike	Strike	Service Item	Early	Middle	Late
		X-ray service			
3.36	3.36	courtesy	3.37	3.39	3.30
3.18	3.15	explanation	3.11	3.17	3.19
3.16	3.07	promptness	3.08	3.17	2.91
		Hospital in general			
3.15	3.04**	comfort of room	3.09	3.03	2.91
3.17	3.20	security	3.30	3.14	3.12
3.39	3.43	courtesy	3.48	3.43	3.34
3.41	3.57***	overall satisfaction	3.60	3.61	3.46

* $p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$.

Discussion

Potential Compounding Factors. Before attempting to interpret the findings, certain potentially compounding factors need to be addressed. One is the difference between the two samples' mean length of stay. Even though median length of stay was quite similar for the two samples, it would appear that a larger proportion of the prestrike sample had very long hospital stays. The effect of this difference was not examined in the present analysis. The other noteworthy difference in the two samples refers to the number of subjects in the strike sample who were interviewed beyond the seventh postdischarge day. When these subjects are removed from the analysis, the overall pattern remains much the same. One exception is with nursing care, in which time of interview reduces three of the items to a point where they are no longer significantly higher than prestrike scores. The absolute value of these strike items remains higher, however. Our ability to analyze the time of interview effect is limited due to our not being able to obtain the precise day on which subjects were interviewed.

Higher Medical and Nursing Scores. The pattern of response of patients to the quality of hospital services provided during the recent strike of hospital employees is varied. Compared with prestrike patient evaluations, some services were evaluated more highly during the strike, others less highly, and still others about the same. Moreover, in some areas of service significant differences were noted between the early strike period and later periods. But at no time did medical or nursing care scores fall below prestrike levels. At all times, medical care items were significantly higher. Nursing care scores declined during the last third of the strike, but not below prestrike levels.

What might account for the fact that patient satisfaction was, for most items, either higher than or on a par with prestrike levels, particularly during the earlier phases of the strike? It must be recalled that this strike was a crisis which did not occur unexpectedly. Prior to its actual onset, the hospital was able to garner resources, plan and otherwise prepare for the emergency. The planning process was able to call upon experience with past strikes to determine the patient services the hospital could sustain at adequate levels of quality. As others (14) have noted, organizational decision making at the onset of a

TABLE 3

Patient Satisfaction Survey: Location-Specific Mean Scores for Services Categories and Prestrike–Strike Differences

	Location									
Service	Medicine		Private		MCH		Surgery		Total	
(items aggregated)	prestrike (N = 138)	strike (N = 166)	prestrike (N = 145)	strike (N = 200)	prestrike (N = 214)	strike (N = 323)	prestrike (N = 147)	strike (N = 219)	prestrike (N = 644)	strike (N = 906)
Medical care	3.31	3.60*	3.43	3.55*	3.45	3.57*	3.43	3.62*	3.43	3.58*
Nursing care	3.06	3.34*	3.16	3.23	3.15	3.23	3.27	3.41*	3.17	3.33*
Housekeeping	2.95	2.86	3.06	2.77*	3.05	2.75*	3.02	2.91*	3.02	2.82*
Dietary	2.66	2.40*	2.52	2.32*	2.62	2.43*	2.74	2.48*	2.61	2.41*
Food delivery	3.00	2.94	2.98	2.80*	3.05	2.93*	3.12	2.99*	3.03	2.92*

* Significant at $p \leq 0.05$.

crisis tends to be effective because competing priorities are subordinated to the primary goals of coping with the emergency.

Group Coping. Groups tend to cope effectively with crisis when members support one another (15). Results of this survey suggest that the onset of the strike coalesced the nonstriking staff in a manner which was evident to patients. Even in cases where patient satisfaction was reported at below prestrike levels, items having to do with interpersonal as opposed to technical aspects generally maintained their former levels. It seems that patients responded favorably to staff attitudes, creating a situation which joined patients and staff members in a common effort to cope with the crisis.

Perceptions of Needs. People can experience a sense of crisis when there is a lack of fit between their perceived needs and commensurate environmental supplies to meet these needs. People can cope, however, by altering their perception of what they need in a given situation (16). In other words, by changing one's subjective perception of the relationship between personal need and environmental capacity for need fulfillment, a defense against crisis can be successfully mounted. While the relatively high satisfaction scores for medical and nursing care may represent an objective increase in the quality of care provided during the strike, it is conceivable that they reflect a sense of reassurance and security among patients that their basic clinical needs would be met in spite of the strike by ancillary and support personnel. Patients' sense of wellbeing may have become crystallized around those aspects of their care which relate specifically to core clinical services.

Length and Uncertainty. Declining satisfaction scores observed in the latter phase of the strike may be attributed not only to the duration of the crisis but also to the uncertainty of its resolution. As the strike persisted beyond what had been experienced in former crises of this type, the hospital became faced with the need to fashion novel solutions for unprecedented problems. The uncertain prospects for ending the strike may well have taken a toll on hard-pressed staff, weary of strike duty and anxious to return to normal social and work responsibilities.

While it is not possible to say with certainty what effects an even longer strike would have on patients' perceptions of their care, the trends indicate that organizational resilience does wear down and at some point may pose a threat to patient wellbeing.

Surveys of Patients. Finally, the findings demonstrate the feasibility and utility of conducting a patient satisfaction survey during a labor crisis. The response rate during the strike was higher than that obtained under normal conditions. The results provide an opportunity to examine a strike experience from the viewpoint of the patient, thus contributing to the institution's ability to respond to similar crises in the future.

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Should Mild Hypertension Be Treated? An Attempted Meta-Analysis of the Clinical Trials

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Abstract

Seven randomized control trials have been published which bear on the question of whether the treatment of mild hypertension (diastolic blood pressure between 90 and 105 mmHg) is beneficial. One study found a slight improvement in mortality, two found statistically significant improvements, three found essentially no difference, and one is still in progress. The benefits of drug treatment for patients with mild hypertension remain unproven. Non-drug therapy has also been insufficiently investigated. Because mild hypertension is so prevalent, the cost to society of additional large-scale trials to resolve the remaining questions is clearly justified by the potential saving of direct and indirect cost.

The value of treatment of mild hypertension (usually defined as diastolic blood pressure in the range of 90–105 mmHg) has been examined in several recent clinical trials (1–7) and has prompted considerable debate (8–12). This paper will critically review the trials and attempt to synthesize the available data. (The combination of the results of separate studies is called meta-analysis).

The hypothesis that treatment of mild hypertension would save lives is a logical outgrowth of two sets of observations, clinical and epidemiologic.

In the period before any treatment was available, the mortality of malignant hypertension was high: 60% to 90% of patients died within two years (13). When ganglion blockers, the first drugs capable of affecting blood pressure, became available, the initial therapeutic use in uncontrolled trials demonstrated improvements in survival. These improvements were so dramatic that most critical observers were convinced of the drugs' efficacy, even without randomized control trials (RCTs).

The next step was the treatment of moderate hypertension, usually defined as diastolic pressures in the range 115–129 mmHg. The disease was less malignant and the importance of well-designed RCTs was increasingly recognized.

Meanwhile, epidemiologic data from the Framingham and other studies was revealing that cardiovascular mortality increased with increasing blood pressure and that there seemed to be no threshold level below which the relationship did not hold. That is, persons with blood pressures of 110/70, for example, had still lower cardiovascular mortality than those with 120/80 blood pressure.

Thus, it seemed important to conduct RCTs to test the hypothesis that lowering mildly elevated blood pressure would lower mortality.

We searched the English-language literature for RCTs in which mild hypertension was treated

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and mortality was measured. The papers were evaluated according to a previously developed scoring system which evaluates important features of study design, blinding, presentation, and analysis of data (14).

The National Library of Medicine database contains more than 300 RCTs of hypertension, but nearly all were short-term studies measuring only blood pressure. We found 7 studies evaluating morbidity and mortality in patients with diastolic pressures in the range of 90–114 (Tables 1–3).

The Studies

The Veterans Administration Study. Begun in 1964, the Veterans Administration (VA) study (1) was the first multicenter trial of the effectiveness of treatment of hypertension in reducing complications. A total of 523 patients with diastolic pressures from 90 to 129 mmHg were randomized to receive hydrochlorothiazide alone or in combination with reserpine, or placebo. The trial was stopped early (average follow-up 20 months) in the patients with diastolic pressure of 115 mmHg or greater because there was a large reduction in cardiovascular complications. The remaining patients completed an average follow-up of 3 years. Overall, the treated group showed a strong trend toward lower mortality and a highly significant reduction in morbidity.

The results, in terms of "total morbid events," were separated into those with moderate (105–114 mmHg) and mild (90–104) hypertension, but morbidity and mortality were not separately reported. The authors concluded that a clear benefit was shown for those patients in the moderate hypertension group, but only a trend for the patients with mild hypertension. A large proportion of the patients randomized had preexisting evidence of target organ damage, and the trial design excluded patients poorly compliant with therapy.

The Public Health Service Trial. The Public Health Service (PHS) randomized placebo—controlled trial (2) was begun in 1966 to provide further information on the benefit of treating mild to moderate hypertension. A total of 389 patients with diastolic blood pressure between 90 and 114 mmHg were randomized to receive chlorothiazide plus reserpine, or placebo. Patients with target organ damage, renal insufficiency, diabetes, and hyperlipidemia were excluded. Patients were followed for an average of 7 years. There was a significant reduction in complications of hypertension in the treated group but no difference in mortality, with only 2 deaths in each group.

The Australian National Blood Pressure Study. The Australian National Blood Pressure Study (ANBPS), a single-blind placebo-controlled trial (3), began in 1973. Patients with diastolic blood pressure between 95 and 109 mmHg without target organ damage were randomized to receive chlorothiazide initially, with additional drugs added in stages as necessary (stage I: methyldopa, propranolol, or pindolol; stage II: hydralazine or clonidine). Patients were followed for an average of 4 years and analyzed both on "intention-to-treat" and "on-treatment" (withdrawals discarded) bases. By both of these methods, total mortality was lower in the treated group, but was statistically significant only for the "on-treatment" analysis.

The Hypertension Detection and Follow-up Program. The Hypertension Detection and Follow-up Program (HDFP) was a large-scale trial (4) of two levels of care—Stepped Care (SC)

TABLE 1
Trial Features

Trial Dates	Entry BP	Pts. with target organ damage	Active Rx (1st step)	Control Rx	Follow-up (yrs)	Blinding	Withdrawal analysis	Quality score
VA 1964–69	90–114 d	included	Hydrochlorothiazide w/wo reserpine	placebo	3	double	discarded	0.77
USPHS 1965–76	90–114 d	excluded	Chlorothiazide & reserpine	placebo	7	double	discarded	0.47
ANBPS 1973–79	95–110 d	excluded	Chlorothiazide	placebo	4	single	both	0.38
HDFP 1973–78	90–104 d	included	Chlorthalidone	referred care (see text)	5	unblind	intention-to-treat	0.55
OSLO 1972–79	95–110 d 150–179 s	excluded	Hydrochlorothiazide	none	5	unblind	intention-to-treat	0.35
MRC 1973–	90–109 d	excluded	Bendrofluazide	placebo	5	single	unknown	0.27
MRFIT 1973–82	90–114 d (62% hypertensive)	excluded	Hydrochlorothiazide	usual care (see text)	7	unblind	intention-to-treat	0.58

Rx = treatment; s = systolic; d = diastolic.

TABLE 2

Trial Results

	Mortality			
	Total		Coronary artery disease	
Trial	Rx	Control	Rx	Control
VA				
no. pts.	10/186	21/194	6/186	11/194
%	5.4	10.8	3.2	5.7
p	0.05		N.S.	
USPHS				
no. pts.	2/193	2/196	2/193	2/196
%	1.0	1.0	1.0	1.0
p	N.S.		N.S.	
ANBPS				
no. pts.	25/1721	35/1706	5/1721	11/1706
%	1.5	2.1	0.3	0.6
p	see text		0.025*	
HDFP				
no. pts.	231/3903	291/3922	86/3903	107/3922
%	5.9	7.4	2.2	2.7
p	0.01*		0.13	
OSLO				
no. pts.	10/406	9/379	6/406	2/379
%	2.5	2.4	1.5	0.53
p	N.S.		0.186	
MRFIT No prev Rx				
no. pts.	90/1987	70/2027	36/1987	31/2027
%	4.5	3.5	1.8	1.5
p	0.081		N.S.	
All pts.				
no. pts.	174/4019	169/3993	80/4019	79/3993
%	4.3	4.2	2.0	2.0
p	N.S.		N.S.	

Rx = treated patients.

Where *p* values were unavailable from published papers, χ^2 was calculated.

* *p* Values from published life table data.

in which patients were assigned to special clinics where hypertension was carefully treated, and Referred Care (RC), in which patients were referred back to local physicians, who treated hypertension as they saw fit. Nearly 5,000 of the 10,940 patients had diastolic pressures in the 90–104 mmHg range. In the SC group they were treated first with chlorthalidone, and a variety of other drugs were added in steps if needed. In the RC group, the majority of patients were given some form of antihypertensive therapy and 30%–50% had blood pressures in the target range at follow-up, compared to 40%–60% at or below goal in the SC group. Overall mortality, which was the primary endpoint, was significantly (20%) lower in the SC group with mild hypertension at the end of 5 years. Data on morbidity have not been published.

The Oslo Study. The Oslo Study (5), a randomized but unblinded trial begun in 1972, compared therapy (starting with hydrochlorothiazide) with no therapy for 785 men with systolic pressures between 150 and 179 mmHg and diastolic pressure below 110 mmHg. At 5 years, mortality rates were nearly identical, but there was a trend toward higher overall morbidity in the control group, with a significantly higher number of nonfatal cerebrovascular events ($p = 0.02$).

Multiple Risk Factor Intervention Trial. An ambitious RCT, the Multiple Risk Factor Intervention Trial (MRFIT), attempted to test whether multifactor intervention could reduce mortality from coronary heart disease (6). Nearly 13,000 men considered to be at high risk for coronary events were assigned either to a special intervention (SI) program of treatment for hypertension (62% had diastolic blood pressure over 90 mmHg), counseling for cigarette smoking, and dietary advice to lower cholesterol, or to usual care (UC) by community physicians. Antihypertensive therapy began with either hydrochlorothiazide or chlorthalidone. Reserpine, hydralazine, guanethidine, or other drugs were added as needed. The results overall showed a slight (7%) reduction in mortality, but the reduction seemed to be due to changes in smoking and in cholesterol. In the patients with hypertension, the mortality was actually marginally higher in the SI than in the UC group. The difference was greatest in the subgroup with resting ECG abnormalities, in which both coronary and total death rates were nearly 50% higher in the SI groups. The authors of the study suggested that this subgroup might have had an unfavorable response to antihypertensive therapy.

The Medical Research Council. In 1973, the Medical Research Council (MRC) began a feasibility study; the design was published (7), but not the results. This led to the commencement of a large-scale (18,000 patients) single-blind study comparing a thiazide (bendrofluazide), a beta-blocker (propranolol) and a placebo in patients with diastolic pressure in the range 90–109 mmHg and systolic pressure below 200 mmHg. Additional drugs were added if needed. The results of the trial are not available at this writing, but the fact that the trial has not been stopped implies that significant differences have not yet been demonstrated.

Evaluation of Quality. Each of the trials was evaluated according to a previously developed scoring system which assigns points to desirable features of blinding, study design, and statistical analysis. The result is a score between 0 and 1.00. The scores of each of the trials are shown in Table 1. They range between .27 and .77; mean score,

TABLE 3
Trial Results

MORBIDITY (NON-FATAL)

Trial	Total		CV Events†		MI		Congestive heart failure	
	Rx	Control	Rx	Control	Rx	Control	Rx	Control
VA								
no. pts.	14/186	37/194	4/186	12/194	5/186	2/194	0/186	6/194
%	7.5	19.1	2.2	6.2	2.7	1.0	0	3.1
p	<0.001		0.05		0.23		.016	
USPHS								
no. pts.	56/193	90/196	0/193	2/196	6/193	5/196	0/193	0/196
%	29.0	45.9	0	1.0	3.1	2.6	0	0
p	<0.001		0.159		N.S.		N.S.	
ANBPS								
no. pts.	113/1721	133/1706	10/1721	16/1706	28/1721	22/1706	3/1721	3/1706
%	6.6	7.8	0.6	0.9	1.6	1.3	0.2	0.2
p	see text		<0.05*		N.S.		N.S.	
HDFP	no measures of morbidity reported							
OSLO								
no. pts.	18/406	28/379	0/406	5/379	8/406	8/379	0/1721	1/1721
%	4.4	7.4	0	1.3	2.0	2.1	0	0.6
p	.08		.02		N.S.		N.S.	
MRFIT	no measures of morbidity reported							

Rx = treated patients.
When p values were unavailable from published papers, χ^2 was calculated.
* p values from published papers.
† Cerebrovascular events (strokes, TIA's, cerebrovascular accidents, or thromboses).

.48. Compared to RCTs we have reviewed in other areas, the hypertension studies were a bit above average in their protocol design and above average in their statistical analysis. Only the two earliest trials, the VA and USPHS studies, were double-blind. Only one, the Australian study, presented data in sufficient detail so that the results could be analyzed both as intention-to-treat and as on-treatment. Intention-to-treat means that all patients are analyzed with the group they are randomized to, whether or not they continue therapy. This approach avoids possible bias in removal of patients but could provide less information about the efficacy of the treatment. The on-treatment approach analyzes only those patients who actually stay on the therapy. This method may not give sufficient weight to treatment failures and side effects. The relative merits of these approaches have been debated (15). We feel that the best approach is to provide sufficient data for both types of analysis.

Discussion

At the present time, 6 trials have been completed, and at least one large-scale study is still in progress. Three trials (VA, ANBPS, and HDFP) showed some benefit in overall mortality for the treatment regimen, and the other three showed essentially no difference. There were important differences in the populations studied in terms of sex distribution, previous treatment for hypertension, and presence of target organ damage, as well as differences in blood pressure criteria for entry. There are major differences in the treatment regimens and even more importantly, in the control regimens. The two large recent trials used community physicians' standard treatment as the control regimen. Their results bear on a different question: Is intensive treatment superior to standard care?

Often, new information can be obtained by pooling the results of prior studies. This process has been called meta-analysis, and it has been used to obtain answers when existing studies were conflicting or too small. However, we must agree with previous analysts (12) that the trials reviewed are too disparate to pool, and that, on the basis of current information, the benefits of drug treatment for patients with diastolic blood pressure in the range 90–105 mmHg remain unproven.

For many years, thiazide diuretics were considered the drug of choice for initial therapy. The

MRFIT study reopened concerns that these drugs' risks may outweigh their benefits, especially in patients with ECG abnormalities. A retrospective subgroup reanalysis of the Oslo study data (16) produced a similar finding. There was a higher number of coronary events in the treated patients with ECG abnormalities at entry than in the control patients with ECG abnormalities at entry. However, a similar analysis of the HDFP data found no such effect (17). In the HDFP patients who met MRFIT eligibility criteria, both those with and without ECG abnormalities had lower mortality on the treatment regimen (Stepped Care) than on the control regimen (Referred Care). Further complicating attempts to answer the question of the adverse effects of the drug is the fact that in MRFIT the clinic physician had the option of prescribing either hydrochlorothiazide or chlorthalidone, while in the HDFP chlorthalidone was the primary oral diuretic. Neither study has published details of the drugs taken by the control patients.

There is considerable evidence that beta blockers reduce the risk of recurrent myocardial infarction in patients who have already had one MI. The possibility that a similar benefit would occur in patients who have not yet had an MI makes these drugs appear more attractive as the first step in treatment of hypertension. Balanced against this possible benefit must be the increased cost of beta blockers. Perhaps the ongoing MRC trial will help to resolve this question.

Another possibility which deserves more attention is non-drug therapy. Numerous modalities, including yoga, muscle relaxation, exercise, salt restriction, weight loss, biofeedback, and meditation have been tried and may have lowered blood pressure, at least in fairly short term studies (weeks to months). A recent review (17) pooled the results of various studies and concluded that weight reduction, yoga, and muscle relaxation clearly produced small, but appreciable, reductions in blood pressure while meditation, exercise training, blood pressure biofeedback, and salt restriction were less effective and not significantly different from placebo. There are no published studies comparing non-drug to drug regimens which measure long-term morbidity and mortality.

Clinical trials of hypertension treatment are costly. Estimates of the number of patients required have varied, depending on the endpoints and length of follow-up chosen, from a few hundred to nearly twenty thousand. The differences observed in the reported trials suggest that an additional trial with slightly over 5,000 patients in each arm would have a 90% probability of detecting a reduction in mortality of 20%, at a 5% level of significance. At a cost of roughly $1,000 to $2,000 per patient per year, a 5-year trial would cost $50 to $100 million.

However, the benefit will outweigh the cost if the trial finds a particular therapy beneficial, if the results of the trial are widely applied by practicing physicians, and if the cost of the therapy is lower than the cost of the untreated disease. In the cost of the therapy should be included the cost of side effects, and in the cost of the disease should be included the cost of lost productivity due to morbidity or premature death. Even if the trial were to show the therapy to be no better than the control, the trial would be worth doing because it could prevent widespread use of a therapeutic regimen whose costs measured in side effects and dollars may be greater than current therapy.

Treatment of hypertension is advocated as a means of lowering the life-threatening complications which may ensue. The cost of these complications includes both direct costs (the expenditures required for their treatment) and indirect costs (the lost productivity due to illness and premature death). The reduction of these costs by treating the maximum number of hypertensives is the return on investment in research on hypertension. Suppose for example that a new therapy will postpone deaths from complications of hypertension so that each hypertensive will enjoy average life expectancy. For each man between the age of 55 and 64 thus saved, an estimated loss of $110,328 in present value of future earnings will be averted. For each woman in the same age group, the estimated averted loss would be $76,574. If the new therapy postpones 60,000 deaths per year, losses of $5–6 billion can be averted. (These present values of future earnings were calculated for 1983 with an interest rate of 8% adjusted for a productivity rise of 2%. The method and data used for the calculation are an update of those used in Ancona Berk, Paringer, and Mushkin [19].)

Patients whose complications do not lead to death incur costs of treatment and lose productive time. Both these costs could also be averted. Against these savings should be put the costs of treatment of hypertension estimated at between $2 billion to $4.6 billion, depending on the proportion of the hypertensive population treated and the treatment regimen (20).

An estimate of the monies that should be available for clinical trials of therapy for hypertension then would be equal to:

Direct costs of treating complications of hypertension

+ Indirect costs (morbidity and mortality costs)

− Cost of treating maximum number of hypertensives.

It is clear that the mortality costs alone would pay for the necessary trial many times over.

We conclude that further trials are justified and that they should evaluate the efficacy of nondrug as well as drug therapy. Both direct and indirect costs should be included in decisions about whether to do trials and how to allocate scarce health care resources.

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Factors Predicting Survival for Six Months After Cardiopulmonary Resuscitation: Multivariate Analysis of a Prospective Study

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Abstract

Factors predicting survival for six months after in-hospital cardiopulmonary arrest were studied in 208 adult patients. Twenty-one were alive six months after the event. Stepwise logistic regression analysis showed cardiac rhythm at initiation of resuscitation, in particular ventricular fibrillation and tachycardia, to be associated with better prognosis than other rhythms. Of arterial blood gas concentrations assessed, acidosis (arterial pH <7.2) at initiation of resuscitation not improved at second arterial blood sampling was found to be negatively associated with survival. Among the medications assessed, sodium bicarbonate and isoproterenol were found to be negatively associated with survival. Neither age, prior medical risk, arterial pO_2, nor arterial pCO_2 were statistically significant in this analysis. Despite the limitations of a small series and of follow-up limited to 6 months, these results can be useful in deciding whether to continue with resuscitation efforts once initiated. The multivariate model correctly predicted survival in 82.1% of patients on the basis of cardiac rhythm at initiation of resuscitation, first and second pH, and use of isoproterenol and sodium bicarbonate.

Since the introduction of external cardiac massage by Kouwenhoven et al in 1960 (1), cardiopulmonary resuscitation has gained wide acceptance. On the basis of recent reports in the literature, one can estimate that cardiopulmonary resuscitation is applied in some 25% to 30% of potential in-hospital deaths (2, 3). Attempted resuscitation is successful in 45% to 50% of cases, but only 8% to 20% of patients survive to discharge (2–5, 7–13). There is concern that the resuscitation of patients suffering cardiac arrest in hospital, particularly patients with end-stage disease, prolongs death rather than extends life.

Several authors have explored the characteristics of successfully resuscitated patients, suggesting that prognosis may differ in the presence of conditions such as malignancy, uremia, coma, underlying coronary artery disease, stroke, cardiogenic shock, and respiratory diseases (6–9). Systematic assessment of these potential predictors has yielded contradictory results (2, 3, 5, 11). Age has also been thought to influence outcome (3, 6), but this association has not been established (2, 4, 5, 11). Clinical factors such as the mechanism of the arrest and arterial blood gases have been reported to influence outcome (4, 7, 8), although their importance has not been clearly established (2, 11). The role of the resuscitation process itself also remains to be confirmed.

Most reported studies address either immediate success of resuscitation (2–6, 11) or survival to discharge from hospital (2, 3, 5–9). Since time to discharge varies from several weeks to several months after resuscitation, the length of survival in these studies is actually not defined. Few in-

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vestigators have followed up patients after discharge (2, 10, 11, 15), and to our knowledge none have systematically analyzed factors prognostic of survival beyond discharge. The present investigation was undertaken to determine by multivariate analysis the relative importance of prognostic factors for survival for six months following arrest in hospitalized patients undergoing cardiopulmonary resuscitation.

Methods

This prospective study was conducted at Beth Israel Medical Center, a 996-bed teaching hospital affiliated with the Mount Sinai School of Medicine in New York City. All patients having cardiac arrest in the hospital during the period February through October 1980 for whom the cardiopulmonary resuscitation team was called were identified. Pediatric patients and patients with primary respiratory arrest were excluded. Cardiopulmonary arrest was deemed to have occurred if a patient was pulseless, without respiration, and unresponsive to shaking and calling. For the purpose of this analysis, only initial arrests occurring in the patient's first hospitalization during the study period were included.

Calls for cardiopulmonary resuscitation (CPR) were ascertained from the page operator and from CPR log books maintained in all clinical units and the Emergency Room. At arrival of the resuscitation team, cardiac rhythm was assessed by electrocardiograph, and arterial blood sampled for determination of blood gases. Information was abstracted from the medical record, from the resuscitation flow sheet, and from laboratory reports of blood gas measurements.

Potentially predictive variables included demographics; procedures and medications used; arterial blood gas determinations during resuscitation; clinical findings at initiation of arrest, namely electrocardiogram and blood gases (pH, pCO_2, pO_2); history of ischemic heart disease; abnormal electrocardiogram prior to cardiac arrest; and prior medical risk, defined as the presence at time of arrest of either cardiogenic shock, stroke with hemiparesis, coma of any etiology, malignancy, uremia, or severe chronic obstructive pulmonary disease.

Long-term outcome was categorized as survival or death within six months of arrest on the basis of evidence in the medical record, by contact with the patient, or from positive information from the physician or a family member. When positive information about status six months after initial arrest was unavailable, status was categorized as unknown.

Data were analyzed by hierarchical stepwise logistic regression using the SAS Logist procedure (14). By this model it is possible to estimate the joint effects of several predictor variables while assuring that those variables logically antecedent to others are retained (15). The hierarchy for this analysis was: characteristics of the patient prior to the arrest, characteristics at time of arrest, and clinical indicators, procedures, and medications during arrest.

Results

Cardiopulmonary arrest occurred in a total of 212 patients during the period of study. Of these, status six months later could be determined for 208. Their median age was 74 years (range 19–99 years); 57% were male. Vital signs were restored and stable for at least one hour in 108 (52%); 75 (36%) died in hospital after resuscitation; 25 (12%) were discharged alive; and 21 (10%) were alive six months after the initial arrest.

The protocol for cardiopulmonary resuscitation, methods of the study, and results of univariate analyses for patients 30 years and older have been published in greater detail in an earlier report (11). Those variables which were statistically significant or approached significance in the earlier analysis (Tables 1, 2) were tested in the stepwise logistic regression.

In the first stage of the regression analysis, characteristics of the patient were assessed. Patients' age and sex, history of ischemic heart disease, and the presence of any of the defined medical risks were not found to be significantly associated with survival for six months after cardiac arrest. The next group of variables assessed were conditions at the outset of resuscitation. Among these, the patients' electrocardiogram at the time the resuscitation was initiated was associated with survival. Blood gas concentrations in arterial blood samples drawn at outset of resuscitation efforts were not found to be significant predictors of survival. Thus, this step in the hierarchical analysis resulted in a prediction model incorporating cardiac rhythm alone, which correctly predicted six-month survival in 50.1% of cases.

In the next stage of the analysis, the significance of blood gas concentrations determined from second arterial blood samples was assessed. Acidosis (arterial pH <7.2) at first sampling was a significant univariate predictor of six-month survival but did not significantly improve the model containing cardiac rhythm. However, the combination of low first pH (<7.2) and failure of

TABLE 1

Characteristics of Patients and 6-Month Survival

Characteristic	No. of pts.	% Surviving 6 mos.
Age (years)		
<64	46	11
65–74	59	17
75–84	76	7
>85	27	4
Sex		
Male	118	12
Female	90	8
Abnormal prior EKG		
Yes	77	14
No	131	8
Cardiac history		
Yes	44	14
No	162	9
Medical risk group		
Yes	91	7
No	117	13

pH to improve during resuscitation added significantly to the multivariate model ($\chi^2_{3df} = 14.27$, $p < 0.005$). The resulting model, incorporating cardiac rhythm at outset of resuscitation and the combination of first and second pH, correctly predicted survival in 69.5% of cases. No significant improvement in this model was achieved with addition of first and second arterial pO_2 or first and second pCO_2.

Finally, we examined whether prediction of survival was significantly improved by the incorporation of use of isoproterenol or sodium bicarbonate into the model. Sodium bicarbonate was more important than isoproterenol, entering the model first ($\chi^2_{1df} = 9.16$, $p < 0.005$). Isoproterenol enhanced prediction significantly ($\chi^2_{1df} = 6.05$, $p < 0.025$). The final model (Table 3) successfully predicted six-month survival of 82.1% of the patients on the basis of EKG, combination of first and second pH, and use of sodium bicarbonate and isoproterenol during resuscitation (model $\chi^2_{8df} = 29.48$, $p < 0.003$). The predicted probabilities of survival under varying conditions in the model are shown in Table 4.

Discussion

This study was conducted to investigate the prognosis for survival for a uniform period of time, 6 months after cardiac arrest, in adult patients in a general acute-care hospital. We have explored by multivariate analysis the relative contributions of patient characteristics, clinical condition at the time of arrest, and conditions during the resuscitation to prediction of survival.

TABLE 2

Characteristics of Arrests and 6-Month Survival

Characteristic	No. of pts.	% Surviving 6 mos.
EKG		
Ventricular fibrillation or tachycardia	36	20
Asystole or bradycardia	82	13
Other	18	0
Not noted	72	12
Low first pH (<7.2)		
Yes	85	7
No	123	12
Low first pH not improved at second pH		
Yes	58	7
No	150	11
First pCO2 <25	38	5
First pCO2 25–50	101	14
First pCO2 >50	69	7
Low first pCO2 not improved at second pCo2		
Yes	30	7
No	178	11
High first pCO2 not improved at second pCO2		
Yes	29	7
No	179	11
Low first pO2 (<25)		
Yes	125	7
No	83	14
Low first pO2 not improved at second pO2		
Yes	65	3
No	143	13
Isoproterenol		
Used	75	1
Not used	133	15
Bicarbonate		
Used	183	7
Not used	25	32

The overall six-month survival in our population (10%) cannot be directly compared to other reports because of the lack of uniformity in length of follow-up. The proportion of our patients surviving to discharge (12%) is similar, however, to other reports, which range from 8% to 20% (2, 3, 5–9).

The lack of a univariate association of characteristics of patients with survival in this study deserves comment. There was a trend toward decreasing survival with advancing age, which is consistent with other reports (5, 6). Those investigators who have tested these trends statistically, however, have not found significant associations (2, 3, 4). The role of patient's age as prognostic of survival remains to be elucidated in a larger study. While medical risk conditions were not significant, specific conditions showed trends consistent with other reports of survival to dis-

TABLE 3
Multiple Logistic Regression Coefficients (B) Predicting 6-Month Survival

Variable	B	SE (B)
Intercept (B)	0.1657	0.6376
Ventricular fibrillation or tachycardia	0.5101	0.6256
Bradycardia or asystole	−0.0852	0.6165
Other EKG	−6.3348	20.6778
First pH <7.2	−0.9797	0.8742
Second pH improved	−1.1662	0.6280
Interaction of first and second pH	1.2013	1.1388
Bicarbonate	−1.6361	0.5727
Isoproterenol	−2.0542	1.0678

TABLE 4
Predicted Probability of Survival in Cardiac Arrest

pH	Bicarbonate	Isoproterenol	Predicted survival
Cardiac rhythm: ventricular fibrillation or ventricular tachycardia			
First pH <7.2			
Second pH not improved	not used	not used	43%
	not used	used	*
	used	not used	13%
	used	used	2%
Second pH improved	not used	not used	42%
	not used	used	*
	used	not used	13%
	used	used	*
First pH ≥7.2			
Second pH not improved	not used	not used	*
	not used	used	*
	used	not used	11%
	used	used	2%
Second pH improved	not used	not used	67%
	not used	used	*
	used	not used	28%
	used	used	*
Cardiac rhythm: bradycardia or asystole			
First pH <7.2			
Second pH not improved	not used	not used	30%
	not used	used	5%
	used	not used	7%
	used	used	1%
Second pH improved	not used	not used	*
	not used	used	5%
	used	not used	7%
	used	used	1%
First pH ≥7.2			
Second pH not improved	not used	not used	25%
	not used	used	4%
	used	not used	6%
	used	used	<1%
Second pH improved	not used	not used	52%
	not used	used	17%
	used	not used	*
	used	used	3%

Other cardiac rhythms: predicted survival equals zero in all circumstances.
* No cases in category.

charge. Patients with malignancy had poorer survival, as has been reported by others (5, 6). Survival in patients with uremia was also observed to be poor, as Johnson et al have noted (8). Because of the small number of patients within groups defined by these conditions, the statistical power of these analyses is poor. The importance of these factors needs to be examined in a larger study before predictions can be made with confidence.

As have others, we have demonstrated that the prognosis for ventricular fibrillation and tachycardia is better than for other mechanisms of arrest (4, 7). In contrast to this report, Bedell and colleagues did not find cardiac rhythm significant in multivariate analysis (2). This may be because they tested it against other intraresuscitation characteristics, rather than considering it antecedent to them as we did. Because cardiac rhythm at the outset of resuscitation to some extent determines procedures during the resuscitation, we retained it in the model and tested the added significance of intraresuscitation predictors.

Holding cardiac rhythm at initiation of resuscitation constant, acidosis (pH <7.2), specifically unimproved pH by second sampling, was associated with poor prognosis. Predicted survival was still worse when sodium bicarbonate or isoproterenol were administered. While sodium bicarbonate may be used in acidosis no matter what the cardiac rhythm, the patients who received it in this study may have had a more severe acidosis than is represented in the cutoff used in this analysis. It should be noted that the resuscitation protocol calls for administration of isoproterenol only in mechanisms other than ventricular fibrillation or tachycardia. The poor survival of patients who received isoproterenol during resuscitation may be attributable to the high oxygen cost of this drug in hearts that are already anoxic or ischemic. In any event, it appears to be an unsuccessful mode of treating asystole and bradycardia. Further, both isoproterenol and sodium bicarbonate are largely used after failure of the patient to respond to initial interventions. It is possible that the worse prognosis associated with these two medications reflects the underlying condition of the patients rather than the deleterious effects of these drugs.

On the other hand Niemann et al (16) have suggested that blood gases may be indicative of the duration of the arrest rather than primary indicators of outcome. An association between duration of the arrest or resuscitation effort and outcome has been reported elsewhere (2). Because of unreliability of estimates of duration in our study, we could not examine the relative importance of these factors.

The results of this study indicate that six-month survival of a substantial proportion of patients (82.1%) can be predicted based on cardiac rhythm, arterial pH, and the use of sodium bicarbonate or isoproterenol or both. These characteristics were associated with wide variation in predicted survival, from 67% in fibrillating/tachycardic patients not acidotic or with corrected acidosis, and not requiring bicarbonate or isoproterenol, to under 1% for patients in whom both bicarbonate and isoproterenol were required.

While the factors described here are useful for predicting survival in hospitalized patients once cardiac arrest has occurred, there remain several areas where further work is needed. In the matter of information available prior to the arrest which can be helpful in deciding whether to attempt resuscitation in the event of a cardiac arrest, this study did not expand the information already available. Physicians, patients, and their families must continue to make these decisions without firm evidence regarding prognosis for survival until a larger study is undertaken. Furthermore, this study has assessed only physical survival. The psychosocial problems of resuscitated patients are still largely undescribed. Expansion and confirmation of the studies by Bedell et al (2) and Bergner et al (17) is in order. The six months of followup in this study, while a uniform time frame, was nevertheless short. Survival and quality of life should be examined in a larger series of patients over a period of years. It would also be of interest to determine if patterns of survival, i.e. survival curves, differ for groups of patients defined by the characteristics described here.

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Patterns of Diazepam Prescribing in Primary Care: A Case Control Study

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Abstract

Diazepam is one of the most frequently prescribed drugs in primary care. Because most research on the patterns of its use have been descriptive, we conducted a survey of the variability of its use by physicians and designed a blinded case-control study to assess the degree to which appropriate indications could be discerned from the chart note. A review of 1,867 consecutive patients seen in a primary care clinic revealed an overall prescription rate of 5.4%, which did not vary by level of physician training but ranged from 0.0% to 14.3% for individual physicians. In the case-control part of the study, appropriate indications for prescription diazepam were documented for 30.8% of those who received diazepam; among those who did not receive any benzodiazepines, 11.6% had documented indications for its use. This suggests that the use of diazepam needs clearer definition in primary care.

Diazepam (Valium) is one of the most frequently prescribed drugs in the United States today (1), as it has been for nearly a decade. In excess of 10% of the adult population uses diazepam or chlordiazepoxide (Librium), most often on a short-term basis (2–4). The most common reported indications for their use are the relief of anxiety and somatic complaints (5–7). Clinical trials have demonstrated that diazepam is effective for the relief of anxiety, although a substantial placebo effect has been found as well (8, 9). However, it has been reported that only about half of those receiving a first prescription of benzodiazepines have a diagnosis of anxiety or psychoneurosis (6). This leaves a large proportion of prescriptions written for either undescribed complaints or complaints for which appropriateness is doubtful. The majority of the prescriptions of psychotherapeutic drugs to outpatients are written by general practitioners and internists rather than psychiatrists (10).

According to Goodman and Gilman (11), benzodiazepines are indicated for the management of anxiety disorder or for the short-term relief of the symptoms of anxiety for the management of, acute alcohol withdrawal, and as an adjunct for the relief of skeletal muscle spasms.

Given the array of physical signs and symptoms of anxiety and given the ubiquity of anxiety in general medical practice (12), the decisions about which patients are candidates for medication and the role of anxiolytic therapy in the overall treatment plan are matters for individually tailored clinical judgment (13). Current recommendations that physicians restrict prescribing to severely anxious patients is as likely to lead to selecting the more persistent or troublesome patient as to selecting the most anxious.

Patients with a depressive syndrome also commonly have agitation, anxiety, or insomnia as a component of the disease. Adjunctive therapy with diazepam may alleviate some of these concurrent symptoms but is generally of little benefit for the underlying depressive disorder (14, 15).

Diazepam has been specifically approved for the treatment of muscle spasms and is extensively prescribed for this purpose (16); however, controlled studies have not found diazepam more effective in the treatment of such common prob-

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lems as low back pain than are conventional measures such as analgesics, rest, and local application of heat.

Diazepam is now used almost exclusively in the treatment of alcohol withdrawal in most medical centers because of its efficacy as well as its relatively low incidence of cardiovascular and respiratory depression, and guidelines for the use of diazepam in this syndrome are now based on well-controlled objective data (17).

It has been suggested that physician attitudes concerning the use of medications to help patients cope with everyday problems and stresses influence their prescribing behavior with respect to these drugs (18). The extent of differences among physicians with respect to their use of diazepam has not been sufficiently examined. Furthermore, studies of prescribing behavior for psychotropic agents are largely descriptive and do not reflect the frequency of somatic complaints and anxiety symptoms seen in practices in general, but rather the frequency with which these complaints are noted among those receiving diazepam. In other words, a controlled study should shed some light on how frequently these prescriptions are written specifically for anxiety and other somatic symptoms, as contrasted to the frequency with which these complaints are seen in primary care practice.

The present study focused on patterns of diazepam prescription. Diazepam was specifically chosen because it is by far the most widely used of all the benzodiazepines. The study addressed the following questions: (a) the frequency and degree of variability in primary care physician prescribing patterns, (b) the medical diagnoses and/or health problems, particularly anxiety, associated with having received a diazepam prescription, and (c) whether, from the progress note of the visit, the appropriateness of diazepam being prescribed as part of the treatment plan could be judged.

Setting

This study was conducted in the Comprehensive Health Service, which is a primary care adult medical outpatient clinic, in a large urban voluntary teaching hospital. The majority of the patient population consists of Medicare and Medicaid recipients. The unit is staffed with full-time and half-time internists as well as medical residents, and operates by the doctor-nurse team concept. Patients are seen by their own physician by appointment but also have walk-in privileges and, thus, see the same physician for continuity of care as much as possible. Prescriptions are usually filled on the same day in the hospital outpatient pharmacy where these prescription records are kept.

Method

The study was conducted in two parts.

Obtaining Physician-Specific Prescribing Rates. The first phase was a simple monitoring of diazepam prescriptions by physicians and relating them to the number of patients seen by these same physicians for a three-month period in order to obtain physician-specific rates of prescription. Sessions with physician absences were excluded from the study in order to eliminate walk-ins seen by physicians other than the patient's own.

Selection of Controls. The second phase was the construction of a case control study involving the identification of two control subjects for each case (diazepam receivers) by selecting the patients seen by the same physician at the same session just before and just after the patient who received a diazepam prescription. If the diazepam-receiving patient was the first or last patient seen during a clinic session, the next two patients either subsequent to or prior to the "case" were chosen. Control patients who received other benzodiazepines were excluded.

The physician note describing the patient visit was then photocopied and the information identifying patient, physician, and medications prescribed were removed. All progress notes were grouped together and equally distributed to members of a review team who coded the health problems as noted, indicated whether any evidence of anxiety had been noted, and used their clinical judgment to determine, without knowledge of actual prescription, whether a diazepam prescription would have been appropriate, based on the physician's progress note.

Scale for Anxiety. A three-point scale was used to score the presence of anxiety: clearly mentioned (anxious, nervous, and so on); possibly present (tense, uncomfortable, and so on); not mentioned. For purposes of analysis only the first category was used.

Scale for Appropriateness of Prescribing Valium. A five-point scale was developed to rate the appropriateness of a diazepam prescription, from "highly appropriate" (rated 1) to "clearly not appropriate" (rated 5). The criteria used were based on the indications, taken as a whole, reviewed earlier in this report.

The review team consisted of three primary care internists, all of whom had worked in the Comprehensive Health Service for between one and six years. Patients seen by the physician review team were excluded from the study.

Pretest for Reliability and Consensus. The reviewing team undertook an initial pretest to measure reliability of abstraction and enhance consensus of judgments of anxiety and appropriateness of valium prescription and uniformity of form completion. The greatest handicap was chart legibility; review of the charts for legibility explained virtually all of the discrepancies noted in diagnostic categories. Judgments of presence of anxiety and appropriateness of prescribing diazepam never differed by more than one point among the three judges. Reliability was judged to be adequate after the trial completion of 60 charts.

All categorical data were analyzed by chi-square, and age differences were assessed by Student *t*-test.

Results

Tabulation of prescription rates by status of physician as either resident or attending showed that these two groups did not differ significantly in rates of diazepam prescription (Table 1). The high degree of variability seen among individual physicians is noteworthy, however, ranging from 14.3% to 0%.

TABLE 1

Valium Prescription Rates by Physician and by Physician Status, Dec. 1979–Feb. 1980

Physician	No. of pts.	No. of Valium Rx	Rate of Valium Rx per 100 pts.
Attendings			
A	340	24	7.1
B	163	6	3.7
C	143	3	2.1
D	147	1	0.7
E	157	13	8.2
F	223	14	6.3
G	385	31	8.0
H	171	1	0.6
SUBTOTAL	1,729	93	5.3
Residents			
I	31	3	9.6
J	14	2	14.3
K	73	3	4.1
L	20	0	0
SUBTOTAL	138	8	5.8
TOTAL	1,867	101	5.4

Attendings vs residents: $\chi^2 = 0.284$, not significant.

Table 2 summarizes the characteristics of the diazepam receivers and their controls. Age and sex differences, although not striking, are consistent with what has been previously reported (5), the recipients being slightly older and more often female. The mention of anxiety or nervousness in the progress note significantly differentiates the two groups well, although this factor was not recorded in 50% of the charts of those who received a prescription. The ICD-CM diagnostic category which was most strongly associated with obtaining a prescription was "neurotic disorders"—noted 45.5% of the time for recipients and 11.4% for controls.

The specific indications noted in the standard pharmacology text, neuroses and musculoskeletal complaints, were noted more frequently among the diazepam receivers than among the control patients. The appropriateness judgments of the raters was also strongly predictive, although the proportion of recipients for whom a prescription was judged "appropriate" (scale ranking 1 and 2) was only approximately 30% and, among those not receiving a benzodiazepine prescription (the controls), nearly 12% were judged appropriate candidates to have received one.

Discussion

In this study, the overall rate of prescribing diazepam was at the lower end of the reported range. Approximately 70% of the diazepam prescriptions examined in this study could not be explained by any criteria as recorded in the medical record. The specific criteria—those relating to specific diagnostic categories referred to in this report as indications—account for approximately one-third of prescriptions. Certainly, vague descriptions of nervousness or anxiety, short of the diagnosis of anxiety neurosis, appear to be the most significant correlate with receiving a diazepam prescription. Even this, however, fails to explain a substantial proportion of those prescriptions written.

It must be remembered that this study was confined to the progress note made on a single visit, and the rationale or justification for a diazepam prescription may have been made during an earlier visit and thus recorded elsewhere in the chart. Lack of complete charting may also account for the apparently low proportion of indications noted on the chart for the "cases" but, as is true for all chart audit studies, this limitation is a reality and one which was quality-of-care implications.

This study was based on a retrospective review

TABLE 2

Characteristics of Valium Receivers and Controls

Characteristic	Valium	Control	p†
Sample size	101	202	
Age: mean ± SD	62.3 ± 18.6	59.4 ± 16.9	NS
Sex: % female	72.3%	60.7%	0.06
Evidence of anxiety, %			
yes	50.5%	29.1%	
no	49.5%	70.9%	<0.001
Appropriateness of Rx			
% highly appropriate 1	18.7%	2.2%	
2	12.1%	9.4%	
3	17.6%	16.0%	
4	12.1%	6.1%	
% highly inappropriate 5	39.6%	66.3%	<0.001
Health problems (ICD-CM codes) noted on progress notes, %*			
Infectious disease (001-139)	2.0%	4.0%	NS
Neoplasm (140-239)	3.0%	1.5%	NS
Endocrine, nutritional, metabolic (240-279)	20.8%	21.3%	NS
Diseases of blood (280-289)	1.0%	5.4%	<0.05
Psychoses (290-299)	0.0%	1.0%	NS
Neurotic disorders (300-316)	45.5%	11.4%	<0.01
Nervous system and sense organs (320-389)	6.9%	4.5%	NS
Circulatory system (390-459)	48.5%	34.2%	<0.05
Respiratory system (460-466)	11.9%	21.8%	<0.05
Digestive system (520-579)	25.7%	25.2%	NS
G-U. system (580-629)	3.0%	7.4%	NS
Skin conditions (680-709)	2.0%	5.4%	NS
Musculoskeletal (710-739)	38.6%	25.7%	<0.05
Other signs and symptoms (780-799)	35.6%	46.5%	NS
No health problem (procedure only) (0.00-0.99)	23.7%	20.9%	NS

* Prevalence rates add to more than 100% because of multiple health problems noted.

† NS, not significant.

of charts, to avoid affecting physician prescribing behavior by awareness of the study's goals.

A large variability was noted among the individual physicians' rates of prescribing diazepam. The tendency to recognize patient anxiety and record it in the progress note is variable (18). This study was designed to overcome this potential problem by selecting as controls, patients seen by the same physician as the diazepam-recipient "cases." In addition, we attempted to avoid a tendency to look more earnestly for evidence of anxiety among diazepam receivers by reviewing the progress notes blindly. Even with these precautionary measures built into the study design, however, a substantial proportion of the prescriptions we studied remain unexplained.

Perhaps a greater issue is what constitutes "appropriate" use. It may be argued that the drug is underused, since the charts of 29.1% of controls recorded anxiety, yet the patient received no benzodiazepines, and 11.6% of the controls were judged to be appropriate candidates for such a prescription. Clearly, however, many patients received diazepam in the absence of documented indications and many did not receive the drug when evidence for its utility was apparently recorded.

Equally noteworthy is the degree of variability between physicians in prescribing diazepam, suggesting substantial variation in attitudes toward the use of psychotropics or varying degrees of physician perception of patient anxiety, or both. It is doubtful whether different patient mixes could explain this degree of prescribing variability, because patients are assigned to physicians in a random way and the age, sex, and ethnicity of the physicians' patient loads are similar.

Further study is needed to examine physician rationale for prescribing diazepam in a primary care setting, with particular focus on arriving at some consensus as to its most appropriate use.

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Education in Community Medicine

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Education in Community Medicine

Perspective

Bessie S. Dana, M.S.S.A.

The educational responsibility of the Department of Community Medicine encompasses undergraduate medical education and residency and fellowship training in general preventive medicine and occupational health. The Education Unit is responsible for the overall planning, development, coordination, and evaluation of this comprehensive educational program. To ensure the integration of teaching activities with service and research, this unit functions as an extension of the Office of the Chairman.

Historically, the need for learning and teaching in community medicine was defined by the founders of the Mount Sinai School of Medicine as essential to the preparation of future members of the health professions. The major focus of early curriculum planning was on educating physicians, with recognition of a future collaborative role in training all disciplines associated with the delivery of health care. This initial interprofessional stance is currently exemplified by departmental involvement in education for social workers and behavioral scientists as well as physicians.

The overall teaching program, in both its design and its implementation, acknowledges that (a) community medicine represents the integration of a body of basic knowledge, attitudes, and skills best represented as the contribution of a multidisciplinary third faculty throughout the entire program of undergraduate and graduate education; (b) effectiveness is dependent on making maximum use of medical center, university, and community resources tailored to the learner's readiness and needs; and (c) there is a baseline competence or standard of excellence for students at each stage of their educational development.

In keeping with these principles, the undergraduate teaching program in community medicine is organized and presented as a continuum of learning and teaching focussed on helping the medical student learn to define health problems in population groups as an integral requirement of his or her general preparation for medicine. Residency and fellowship training, guided by these same principles, is organized as an integrated program of didactic and experiential learning, designed to prepare its graduates for the variety of new and changing career opportunities that require the integration of population medicine with clinical medicine, such as health care planning, management, and research and clinical epidemiology as well as public health practice.

The faculty responsible for the design and implementation of the educational program represents those professions and disciplines—medicine, social work, behavioral and environmental sciences, and epidemiology—essential to the achievement of the central aim of the department to help students understand and deal with health problems in population groups. Epidemiology serves as the basic science underpinning for the department's undergraduate medical school teaching and its residency training program. Epidemiology, as basic science and method, also strongly influences the department's graduate and postgraduate teaching programs for nonmedical personnel. The various teaching activities of the department are further unified by joining the responsibilities for curriculum development with faculty development; by the general commitment

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of the faculty to student-centered learning; by the emphasis on inductive rather than deductive teaching that follows from such a commitment; and by maintaining close linkages with colleagues in the medical school, the university, and community-based health and health-related programs in planning and offering didactic and experiential learning opportunities.

The four papers that follow represent the outgrowth of a continuing effort to integrate the forces of clinical and population medicine in the pursuit of more precise understanding of the complex health problems that confront contemporary society. They exemplify the power of epidemiology to give direction to the learner's intellectual curiosity, structure to his or her search for truth, and a sense of his or her right to membership in the community of science.

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Primary Care of Elderly Women: Is Pap Smear Screening Necessary?

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Abstract

The American Cancer Society currently recommends Pap smear screening for cervical cancer every three years until the age of 65 and no screening thereafter. However, elderly women have a high rate of prior nonuse and underuse of Pap smear screening. Women over 65 who do participate in screening programs are two to three times more likely to have abnormal Pap smears than are women under 65. These elderly women seek greater than 98% of their health care from primary care providers as opposed to gynecologists. To begin to assess both the gynecologic health of elderly women and the need for primary care practitioners to perform Pap smears on these patients, a pilot gynecology screening program was initiated in an urban ambulatory primary care clinic with a large elderly population. Analysis of data from 205 patients, 37% of them over the age of 65, showed a strong positive linear relationship between age and median interval since prior Pap smear (correlation coef. $r = .93$). Overall, 64% of the elderly women screened had either never had a Pap smear or had not had one within three years. The prevalence rate of positive Pap smears was 27/1,000 for women 65 or older. It is hypothesized that this high prevalence rate is, in part, related to the low prior use of screening by elderly women. These findings suggest that primary care practitioners need to consider these use patterns when applying the current recommendations for cervical cancer screening to older women.

Elderly women have been found to be two (1) to three (2) times more likely to have abnormal Pap smears (for carcinoma-in-situ and invasive carcinoma of the cervix) than women under 65. The elderly population accounts for 25% of the total incidence of invasive cervical cancer (3). Current guidelines for Pap smear screening, however, recommend the cessation of screening at age 60 (4), 65 (5), or 70 (6, 7). These upper age limits are justified by quoting the low age-specific conversion rates from negative to positive Pap smears for carcinoma-in-situ in the elderly age group that was studied in British Columbia (6). These conversion rates were determined in a population of women who had previously received regular Pap smear screening. In that study, elderly women were underrepresented in screening relative to their proportion in the general female population of British Columbia (7). Other studies (1, 2, 8) have similarly noted the underrepresentation of the elderly in screening programs.

Increasing age has also been found to be related to decreasing use of Pap smear screening (2, 9, 10). It has been reported that from 28% (9) to 41% (3) of elderly women have not had a recent Pap smear. A U.S. National Health Survey (3) found that as many as 40% of women over 65 have never had a Pap smear. Women who have never had a Pap smear have been found to have an incidence of cervical cancer 2.7 (11) to four (8, 12) times

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higher than that of women who have had at least one Pap smear.

The current American Cancer Society recommendation for the cessation of Pap smear screening at age 65 assumes frequent screening prior to that age (5). Often physicians, when applying these recommendations, do not take into account the high rate of prior nonparticipation in, and underuse of, Pap smear screening by this older age group.

As previously noted, elderly women are more likely than younger women to have an abnormal Pap smear when they are screened. However, elderly women tend not to utilize screening services; when they do seek health care they generally see primary care physicians rather than gynecologists (9). A primary care setting, then, is the logical one in which to explore the need for Pap smears for older women.

This paper is a preliminary report on the gynecological health status of women attending an urban medical primary care clinic which serves a predominantly elderly population, presenting prior Pap smear screening patterns and the yield of abnormal Pap smears in this population.

Methods

Data were collected on women receiving ongoing health care in the Medical Primary Care Unit at City Hospital Center at Elmhurst. The unit is an outpatient medical clinic providing comprehensive, continuous, primary care to over 9,000 patients per year with chronic medical illnesses. Approximately 44% of the patients are white, 38% are Hispanic, 16% are black, and 2% are Oriental. Women constitute 68% of the overall patient population. Women 65 years or older (hereafter referred to as "elderly" women) constitute 55% of the female patient population. The average age of the female patients in the clinic is between 60 and 65 years.

A weekly gynecology screening session was established in the Medical Primary Care Unit. During this screening session, information on gynecologic health status was collected, and Pap smears were performed, regardless of the patient's age. This session served as both a primary care service to the patients and a teaching session for primary care internal medicine residents; only six to seven patients were scheduled per week. All unit staff (nurses, attendings, and internal medicine housestaff) were informed of the availability of this new session and were asked to refer their patients for routine gynecologic screening. From September 1981 to August 1983, 205 women attended the screening sessions.

On all patients, a complete gynecologic history was obtained, a pelvic and breast examination was performed, and a Pap smear obtained. All examinations were performed, or directly supervised, by one of the authors (JSM). Pap smears were obtained by scraping the cervical canal and posterior vaginal fornix with an Ayre's spatula. When no cervix was present, vaginal vault smears were obtained. Slides were sprayed immediately with an aerosol water-soluble fixative and sent to the hospital's cytology laboratory for interpretation. The laboratory reported the results of Pap smears as follows: Class I, negative, including negative with inflammation, *Trichomonas, Monilia,* cocci, or herpes; Class II, atypia, not inflammatory; Class III, suspicious for malignancy, including cervical intraepithelial neoplasia; Class IV, positive for malignancy.

In this study, a "positive" Pap smear was defined as a Class III or Class IV report. Abnormal findings were followed up as appropriate. Liaison with the Department of Obstetrics and Gynecology was established.

The data were analyzed on a microcomputer using the Lotus 1-2-3 Spread Sheet. Statistical calculations were performed using standard formulas.

Results

Demography. The age distribution of the patients (n = 205) screened is shown in Table 1. The mean age was 57, the median 58, with a range of 18 to 89 years. Elderly women (n = 76) constituted 37% of the sample. Grandmultiparous (gravida 5 or more) women constituted 19.5% of the total study population and 19.7% of the elderly population. All patients were in lower-income groups.

History. Based on their gynecologic history, 87% of the patients were asymptomatic for gy-

TABLE 1
Age Distribution

Age	Number	Percent
15–24	6	2.9
25–34	10	4.9
35–44	28	13.7
45–54	42	20.5
55–64	43	21.0
65–74	50	24.4
75–84	21	10.2
≥85	5	2.4
TOTAL	205	100

necologic complaints. Of the remaining 13% who reported symptoms at the time of examination, two thirds were under 65. Postmenopausal bleeding was the initial complaint for five of the eight elderly patients who reported symptoms (Table 2).

Of the 205, 175 patients reported a prior Pap smear and 25 reported never having had a Pap smear; no information was available for 5. Among the 175 patients with a prior Pap smear there was a strong positive linear relationship between age and median interval since prior Pap smear (correlation coefficient r = .93, Fig. 1). The elderly reported a median interval of 5 years since their most recent Pap smear.

Of the 25 patients reporting never having had a Pap smear, 3 were young women who had not become sexually active, and for whom a Pap smear was not yet indicated. Of the remaining patients for whom a Pap smear was indicated but never performed, 45% were elderly.

Fig. 2 summarizes overall use, by age, of prior Pap screen for the sample population. In the elderly group, only 36% of the women reported having had a Pap smear within the past three years, 51% reported having a Pap smear more than three years ago, and 13% reported never having had a Pap smear. Overall, 64% of the elderly women screened had either never had a Pap smear or had not had one in the preceding three years.

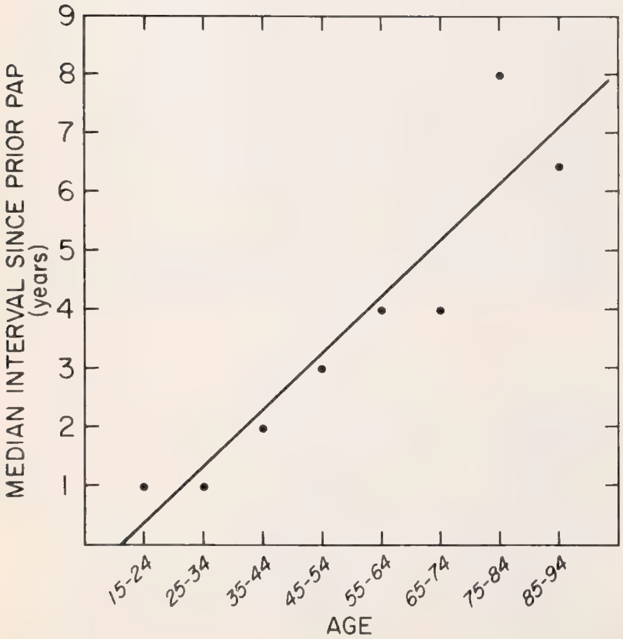

Fig. 1. Strong positive linear relationship between age and median interval since prior Pap smear (r = .93).

TABLE 2

Presenting Symptoms

Symptom	<65 yrs.	≥65 yrs.
Postmenopausal bleeding	3/8	5/8
Vaginal discharge	4/5	1/5
Chronic pelvic pain	5/5	0/5
Menstrual disorder	3/3	0/3
Incontinence	1/2	1/2
Dyspareunia	0/1	1/1
Abdominal mass	1/1	0/1
Vulvar pruritis	1/1	0/1
TOTAL	18/26	8/26

Physical Examination. Physical examination of the 205 patients revealed 120 abnormal findings among 86 patients (Table 3).

Cytology. Two hundred Pap smears were performed. All smears were reported as technically satisfactory. Five patients refused examination; three of these were elderly, and two of these had never had a Pap smear. Of the 200 Pap smears, 195 were Class I, one was Class II, and four were Class III or IV. Two of the positive smears (Table 4) occurred among the 73 elderly patients examined, yielding a prevalence rate of 27/1,000 Pap smears in this age group (95% confidence interval −11 to +65/1,000), compared to a prevalence rate of 16/1,000 abnormal smears in the under-65-year-old group (95% confidence interval 0–37/1,000). In this small sample, the difference between these two groups is not statistically significant.

Diagnoses. Many diagnoses were noted in the study group (Table 5). Fourteen percent of the patients had had hysterectomies. In the elderly,

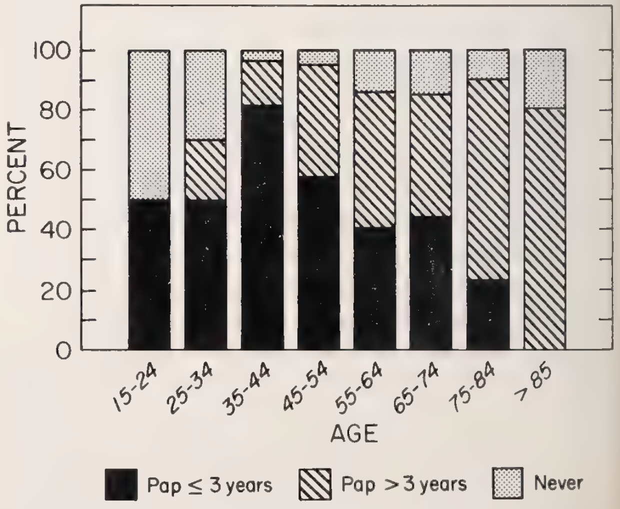

Fig. 2. Overall use, by age, of prior Pap smear. Three ranked categories were chosen as consistent with American Cancer Society recommendations for screening (5).

TABLE 3
Abnormal Findings on Physical Examination

Findings	<65 yrs.	≥65 yrs.
Cystorectocele	25/39	14/39
Vaginitis, all types	13/18	5/18
Abnormal-appearing cervix, all types	13/15	2/15
Abnormal uterus, all types	10/12	2/12
Fibrocystic breast disease	7/9	2/9
Adnexal mass	5/7	2/7
Vulvar inflammation, all types	2/6	4/6
Endocervical polyp	3/4	1/4
Uterine prolapse	0/3	3/3
Rectal mass	1/2	1/2
Condyloma accuminata	2/2	0/2
Vaginal polyp	0/1	1/1
Urethral carbuncle	1/1	0/1
S/P radical mastectomy	1/1	0/1
TOTAL NO. OF FINDINGS	83/120	37/120

85% of the hysterectomies were partial; in the younger women, 67% were. One of the abnormal Pap smears occurred in a woman who had a total hysterectomy. On biopsy this proved to be an early vaginal squamous cell carcinoma.

Follow-up. On the basis of the history, physical examination, or cytology results, follow-up was recommended for 15 elderly patients and 23 younger patients. One third of the elderly patients complied with the recommendation, 47% missed their appointment, and 20% overtly refused. Of those under 65 years old, 65% complied and 35% missed their appointment; none refused. The elderly women studied, then, complied with the recommended follow-up only half as often as did the younger women.

Discussion

In this preliminary study we observed trends in history, physical examination, diagnoses, and follow-up. Eighty-seven percent of the patients were asymptomatic. Postmenopausal bleeding was the major symptom among elderly women who had any symptoms. Of the wide range of diagnoses, cystorectocele and vaginitis were the two most common. The elderly complied with follow-up only one-half as often as the younger patients.

A striking use pattern with respect to age was noted. The older the patient, the longer the interval since her previous Pap smear. Overall, 64% of the elderly patients had either not had a Pap smear within three years, or had never had one at all.

The prevalence rate of 27/1,000 abnormal smears in our elderly population is higher than the rates noted in other studies.

Our study may have been influenced by several factors, including the demographic characteristics of our population, the age-specific rate of participation in screening, selection biases, and compliance with follow-up. Our patient population is an ethnically diverse, urban, and generally lower-income population. More than half of the patients in the clinic are Hispanic or black, the majority of the Hispanic population consisting of recent immigrants from Central and South America. Black and Hispanic women are known to be at high risk for the development of cervical cancer (10, 13–15). Living in an urban environment and being in a lower-income group are also considered risk factors for the development of cervical cancer.

Our study population is representative of our general female population in the clinic with respect to the risk factors, but the elderly are underrepresented and the younger women are overrepresented in our sample. This underrepresentation of older women in screening programs has been noted in a variety of other settings. In three

TABLE 4
Characteristics of 4 Patients with Positive Pap Smears

Age	Years Since Pap	Symptoms	Physical Examination	Pap Class	Pathologic Diagnosis	Follow-up
47	4	none	normal; S/P TAH & BSO	III	vaginal squamous cell carcinoma	c, vaginal biopsy, vaginoplasty
52	5	PMB	abnormal	IV	CIN, 3	c, bx, D&C, TAH & BSO
72	5	PMB	abnormal	III	CIN, 1	c, bx, D&C, TAH & BSO
85	5	PMB	normal	IV	invasive cervical squamous cell carcinoma	refused

Abbreviations: bx, cervical biopsy; c, coloposcopy; CIN, cervical intraepithelial neoplasia; D&C, "vabra" endometrial aspiration; PMB, post-menopausal bleeding; TAH & BSO, total abdominal hysterectomy and bilateral salpingo-oopherectomy.

TABLE 5
Diagnoses

Diagnosis	<65 yrs.	>65 yrs.
Normal examination*	73	48
S/P hysterectomy		
partial	12	9
total	6	2
Vaginitis		
monilia	9	4
atrophic	3	0
trichomonas	1	0
Chronic cervicitis	2	0
Leiomyoma	8	2
Cervical atypia/dysplasia	1	0
Cervical CA		
in situ	1	1
invasive	0	1
Vaginal CA	1	0
Colorectal CA	1	0
Chronic pelvic pain syndrome	4	0
Endocervical polyp	2	1
Primary infertility	2	0
Uterine prolapse	0	2
Follow-up refused		
PMB	1	2
adnexal mass	0	1
Other**	2	3
TOTAL	129	76

* Includes fibrocystic breast disease and cystorectocele.

** Lichen sclerosis atrophicus, nonspecific vulvar inflammation, neurodermatitis, urethral carbuncle, benign vaginal polyp.

Swedish counties (8), screening reached one-quarter of women over age 70 and one-half of women from ages 60 to 69. In a British Columbia study (6) only 12% of the population (of women over 60) was represented in screening in 1966.

This relative nonparticipation is likely to lead to an underestimation of the prevalence of abnormal Pap smears in the elderly. Many studies (8, 11, 12) have demonstrated that nonparticipants in screening are at high risk for the development of cervical cancer. In the Swedish study (8) 85% of the total nonparticipants in screening were over age 60. When this age group, which constitutes 40% of the total female population in the counties studied, was screened it contributed a disproportionate 67% of the reported cases of invasive cervical cancer. In the United States, screened elderly women had two (1) to three (2) times more abnormal Pap smears than women under 65.

Our methods of sample selection may have also influenced the results of the study. Referral to screening was not random and may have been influenced by the presence of gynecologic symptoms, patient acceptance, or physician behavior. In the sample, 13% of the women complained of gynecologic symptoms, 7% of the elderly having postmenopausal bleeding. No information is available on the incidence and types of gynecologic symptoms in our general female patient population. In a mass screening program in Norway (16), gynecologic symptoms were not found to be predictive of abnormal Pap smears. However, in that study only women up to age 61 were screened. Although both elderly women with abnormal Pap smears in our study did complain of postmenopausal bleeding, they represent too small a sample from which to generalize about the predictive value of postmenopausal bleeding or its influence on the prevalence rate of abnormal Pap smears. Other studies (2, 6) of larger samples of women in this age group give no information on presence of gynecologic symptoms. Further research is necessary to determine the effects of abnormal gynecologic symptoms on the prevalence of abnormal Pap smears in elderly populations.

Selection biases in our sample may have also occurred through the interaction of patient acceptance and physician behavior. The "no-show" rate of the gynecology screening session was comparable to that of the entire clinic (33%). However, we do not know how many women refused appointments and whether they differed from the women who accepted appointments. Within this latter group, those women who kept their appointments may have differed from those who did not.

Physicians may have been more likely to refer women at higher risk to screening than women at lower risk. When physicians either recommend (9) or perform (17, 18) Pap smears, they achieve a high degree of compliance. In our study these effects may have resulted in a confounding of screening for cervical cancer with case-finding. This effect would tend to overestimate the true prevalence of abnormal Pap smears in our clinic population.

The prevalence rate of positive Pap smears may also have been influenced by noncompliance with follow-up. The observation that both elderly women with positive Pap smears had had a Pap smear five years previously suggests a possible failure of adequate follow-up of those prior smears. The elderly women in the study complied with follow-up less than one-half as often as the younger women. Inadequate follow-up has been noted as a problem in other cervical cancer screening programs (19). Age was only one factor which may have influenced compliance with follow-up in our study. It would be important to elucidate other factors influencing compliance to further improve the effectiveness of cervical cancer screening programs.

Despite the methodological limitations of our study, this pilot screening program for women in a primary care setting revealed several important trends in the prevalence of abnormal Pap smears and the utilization of screening by the elderly. This is the first study which explored the screening of elderly women in a nongynecologic out-patient primary care setting. Our prevalence rate of 27/1,000 abnormal Pap smears in elderly women is higher than the rates observed in other settings. Other studies have reported prevalence rates of from 4.8 to 7.4/1,000 abnormal Pap smears in older women (1, 2, 20–22). It is difficult, however, to compare the prevalence rates observed in these studies to our prevalence rate. These studies present no information with which to assess the symptomaticity of their samples, the age-specific rates of screening among their population, or the effects of the setting itself on selection biases.

The high prevalence rate of abnormal Pap smears in elderly women noted in our primary care setting was coupled with a concurrent observation of a low overall use of prior Pap smear screening in this age group. One reason for this low use may be that the current elderly population was beginning to move out of their reproductive years when the Papanicolaou smear was first widely used in screening for early detection of cervical cancer. These postmenopausal women may not have sought routine gynecologic care after their reproductive years (9).

In addition to the decreasing use of screening with increasing age in our, and other, studies (2, 9, 10), many women have never had a Pap smear at all. In our sample 13% of the elderly women had never had a prior Pap test. Other studies have noted a wide range in the percentages of elderly women who have never had a Pap smear. O'Rourke noted that 5% of women ⩾ age 60 who agreed to participate in the screening had never had a Pap smear; however, she reports no data on the 50% of her sample who declined to participate in screening (23). Celentano reported that 14% of the women age 65–74, and 38% of the women over 75 he interviewed had never had a Pap smear (9). The U.S. National Health Survey of 1977 reported that as many as 40% of the elderly women surveyed had never had a Pap smear (3). In Buffalo, NY, Warnecke and Graham noted that 61% of the women over 65 reported no prior screening (10). This wide range observed in the percentages of elderly women who have never had a Pap smear most likely represents inherent differences among the samples with regard to education, socioeconomic status, access to health care and methods of sample selection.

Based on the results of this study of women in an outpatient setting, our hypothesis is that the current elderly cohort is at high risk to develop cervical cancer because of a lifelong nonuse and underuse of screening. This hypothesis is supported by several other studies. The Massachusetts Department of Public Health survey (2) noted that the number of women who underwent a Pap test decreased with age, despite both the high yield of positive smears in the elderly and the increase in the death rate from cervical cancer with age. Several studies have observed that women who have never had a Pap test are at high risk for the development of cervical cancer (8, 11, 12). One of these studies (8) noted that 85% of the nonparticipants in Pap smear screening were over age 60. However, nonparticipants in prior Pap smear screening have generally used health care services (24–26).

The results of this and other studies argue for providing more Pap smear screening in nongynecologic primary care settings. These results also raise questions about the assumed lack of need to target screening to women over 65.

The American Cancer Society (5) recommends that women who have been regularly screened prior to age 65 should not be screened, and that women who have never had a Pap smear be screened regardless of age. For women who have been infrequently screened prior to age 65, there are few guidelines. The National Institutes of Health (27) suggests that a woman have two negative Pap smears after age 60 before screening can cease.

As many as 70% of women over 65 in the U.S. today may never have had, or have only infrequently had, a Pap smear (3, 9). Further research is needed to confirm this possibility. If it is confirmed, elderly women would constitute a high-risk group for the development of cervical cancer. We are currently conducting a screening program for the entire elderly female population attending the unit to explore these issues further.

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The Prevalence of Alcoholism in Acute Care General Hospital Patients

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Abstract

Reported prevalence rates of alcoholism in hospitalized patients range from 9% to 55%. A comprehensive study of the broad cross-section of the acute-care general hospital patient population is needed to yield a more accurate prevalence rate. Therefore, a prospective prevalence study was undertaken at Beth Israel Hospital, and a 10% sample of patients admitted over a 2-month period was interviewed. The interview consisted of 2 validated screening tools: the 10-question brief Michigan Alcoholism Screening Test (b-MAST), and the 4-item CAGE questionnaire, plus additional lifestyle questions. Of the 500 individuals selected, 368 were interviewed. Both the b-MAST and CAGE yielded similar alcoholism prevalence rates, 7% and 8% respectively. The high-risk groups were males, service cases, and those with a positive smoking or illicit drug history. When the whole spectrum of the acute-care general hospital patient population was screened for alcoholism, the group as a whole was not found to be at high risk. Many prior studies actually screened high-risk subgroups of the acute-care general hospital patient population, yielding high prevalence rates of alcoholism. These prior reported rates for high-risk subgroups were consistent with rates for the corresponding subgroup in this study. Therefore, alcoholism screening programs should be targeted to the high-risk subgroups identified in this study, for example male service patients. Programs should incorporate the available treatment facilities and intervention should be initiated early in the hospital stay. Only one of the two screening tools need be used, since both were found to be reliable.

While an estimated 10% of the United States population has a drinking problem (1, 2), studies have reported that anywhere from 9% to 55% of hospitalized patients are alcoholics (3–5). These studies have varied in design, sample size, type of hospital setting, and screening tools. The studies tended to focus on service patients and males on medical and surgical services, predominantly at Veterans Administration, city, and military hospitals, where the alcoholism prevalence may have been greater. The prominence of alcoholism as a problem in these settings may have been the impetus for the study in the first place. Most of the studies have used interview rather than chart review techniques. However, very few of the studies have used validated screening tests (6).

There is a definite need for a more comprehensive study, which would examine a broader cross section of the acute-care general hospital patient population, using and comparing multiple screening tools. This would yield a more accurate estimate of the prevalence of alcoholism in this population and determine whether this group is, indeed, at high risk for alcoholism.

Many issues in alcoholism etiology are unresolved (7); nevertheless alcoholism is associated with a broad spectrum of disease. Fifty percent of male heavy drinkers, defined as those who drink more than 80 grams of pure alcohol per day, develop serious physical disease. Yet there may be no effect on their psychological or social functioning. Women tend to be more susceptible to the associated physical disease (2). On the other hand, the problem drinker has a pathological dependence on alcohol and drinks despite resultant physical, social, or psychological problems (8).

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The acute-care general hospital is a critical site for identification of alcoholism and subsequent appropriate referral. The patients may be more receptive to intervention during their hospitalization. As well, the early identification of alcoholism may play an important role in both the diagnosis and treatment of the presenting illness.

A prospective prevalence study was undertaken at Beth Israel Hospital to estimate the prevalence of alcoholism in its patient population using 2 screening tools. The risk factors associated with alcoholism in this population were investigated.

Methods

Beth Israel Hospital is a voluntary 692-bed acute-care hospital in lower Manhattan which serves the East Village, Lower East Side, Williamsburg, and other boroughs of New York City. It is affiliated with Mount Sinai School of Medicine as well as Bernstein Institute, a major drug and alcohol detoxification treatment center.

Case Selection. Every tenth patient admitted to the hospital from June 6, 1983 to August 4, 1983, to a total of 500 cases, was invited to participate in the study. The cases were chosen using a daily computer listing of admissions entered as a room was assigned to them. All pediatric cases (under age 18) were excluded and replaced by the next admission in the computer printout. Only patients with at least an overnight hospital stay were included.

Screening Tools. Most screening tools for alcoholism are questionnaires administered by an interviewer (9). The best known is the Michigan Alcoholism Screening Test (MAST), a 25-item interview questionnaire (10). In 1972, Pokorny chose the 10 most discriminating questions from Selzer's data to develop the brief MAST (b-MAST) (11). The scores of the two tests had excellent correlation. The b-MAST was found to be as good as the MAST and superior when brevity was desirable. The CAGE questionnaire is an alcoholism screening test consisting of 4 nonincriminating questions on the need to *c*ut down drinking, *a*nnoyance at criticism of others, *g*uilt, and the need for *e*yeopeners (hence the acronym CAGE). The test was brief and easy to administer (12).

The interview for this study consisted of the two most commonly used and previously validated screening tools: the 10-question b-MAST and the 4-item CAGE questionnaire plus additional lifestyle questions on occupation, smoking, drinking, and illicit drug history.

Data Collection. If the patient was a private case, the attending physician was contacted for permission for an interview. For nonprivate patients, permission to conduct the interview was obtained from the house officer in charge of the case. When permission was acquired, the patient was approached, participation in the study was explained as voluntary, and consent to be interviewed was asked for. The private attendings, housestaff, and patients were not informed of the precise purpose of the study, and were told that the questionnaire surveyed lifestyle patterns of the patient population. The interviews were conducted by four specially trained college students, one Spanish speaking. For patients not fluent in English or Spanish, an interpreter was used.

Basic demographic data were collected, including sex, race, occupation, education, service, admission type (emergency or elective), private or service status, and insurance type. Questions on smoking, drinking, and illicit drug use were asked. The specific interviewer involved, the language in which the questionnaire was administered, and the number of people present in the room were recorded.

To examine for sequence effect, the CAGE and b-MAST were randomly administered first or second in the interview, depending on whether the admission number of the particular case was odd or even. This was begun on case number 203.

Data Analysis. The data collected from the interviews were coded and entered onto the computer at Mount Sinai School of Medicine. The χ^2 test was used with a significance level of 0.05. Reliability of the 2 screening tools was estimated with the determination of Kappa, which yields a measure of the degree of the agreement between the 2 tests corrected for chance (13).

Due to the small sample size, each variable had to be analyzed one at a time by univariate rather than multivariate analysis. The results should be reviewed with this in mind; not all potential confounders may have been controlled for.

Results

Of the 500 persons selected, 12 were excluded as a cancelled admission or shorter than overnight stay. Of the 488 remaining, 368 patients (75%) were interviewed (Table 1).

The demographic profile of interviewees (Table 2) was similar to noninterviewees. Both groups were predominantly white, female private patients electively admitted to Medicine, Obstetrics-Gynecology, and Surgery services. Patients of all degrees of illness were included in the study, including 14 cases in intensive care (3%).

Eighty-seven percent of the interviews were conducted in English. Other languages included

TABLE 1
Reasons for Not Interviewing

	No. (%)
Patient discharged before interview	39 (8)
M.D. permission not granted by time of discharge	20 (4)
M.D. permission not granted	18 (4)
Patient refusal to be interviewed	14 (3)
Patient incompetent mentally/physically	13 (3)
Patient signed against medical advice	10 (2)
Patient died early in hospitalization	4 (1)
Patient refusal to complete interview	2 (0)
TOTAL	120 (25)

TABLE 2
Patient Demographics

	No. (%)		No. (%)
Sex		Service	
Female	241 (65)	Medicine	99 (27)
Male	127 (35)	Obstetrics	73 (20)
Race		Gynecology	43 (12)
White	237 (64)	Surgery	59 (16)
Hispanic	74 (20)	Urology	29 (8)
Black	31 (9)	Neurosurgery	14 (4)
Oriental	16 (4)	Head-Neck	12 (3)
West Indian	6 (2)	Psychiatry	11 (3)
Other	3 (1)	Plastic surgery	7 (2)
Unknown	1 (0)	Ophthalmology	7 (2)
Admission type		Neurology	4 (1)
Elective	239 (65)	Dentistry	3 (1)
Emergency	117 (32)	ENT	2 (1)
Urgent	12 (3)	Vascular surgery	2 (1)
Insurance type		Rehab. med.	2 (1)
Blue Cross	121 (33)	Unknown	1 (0)
Medicare	107 (29)	Patient type	
Medicaid	76 (21)	Private	279 (76)
Private ins.	31 (8)	Service	88 (24)
Patient pay	25 (7)	Unknown	1 (0)
Workmen's comp.	8 (2)		

Spanish (6%), Yiddish (2%), Chinese (2%), and Russian (2%). The CAGE questionnaire was administered preceding the b-MAST in 124 interviews (34%), following it in 244 cases (66%). Each of the 4 college students interviewed 21% to 32% of the patients.

Prevalence of Alcoholism. The overall estimated prevalence rate of alcoholism determined by the b-MAST was 7% and by the CAGE questionnaire 8%. The rates were the same whichever was administered first. Results of both questionnaires were in the alcoholic range for 16 cases (4%). Forty cases (11%) were determined to be alcoholic by either one or the other questionnaire. Though the prevalence rates determined by the two questionnaires were similar, some of the cases selected as alcoholic by the two tests were different. However, the agreement of the 2 tests was found to be significantly better than chance alone (Table 3).

Smoking and Drug Use. When asked, 58% of patients said that they had drunk alcohol at some time; 38% of interviewees denied use of alcohol. Of the total, 47% were current or exsmokers; 16% admitted to present or past illicit drug use; 14% used marijuana, 7% cocaine, 3% heroin, and 2% were on methadone maintenance prior to current hospitalization.

Alcoholism Prevalence Rates in Risk Groups. The prevalence rates of alcoholism of the different demographic categories were examined. Males were found to have a significantly higher prevalence rate determined by both questionnaires (b-MAST 13%, CAGE 15%) than the females (b-MAST 4%, CAGE 5%). The prevalence rates of alcoholism for service cases were 14% by b-MAST and 13% by CAGE, significantly higher than the percentage of private cases found to be alcoholic by the b-MAST (5%). Among the male service cases, 25% by b-MAST and 21% by CAGE were alcoholic. The rate for female service cases was 8% (Table 4).

TABLE 3
Reliability Testing of the b-Mast and Cage

	CAGE		
b-Mast	Alcoholic	Nonalcoholic	Total
Alcoholic	16	10	26
Nonalcoholic	14	328	342
TOTAL	30	338	368

Kappa = 0.54 with $p < 0.001$.

When the various insurance types were examined, the prevalence rates of alcoholism were significantly different by both questionnaires. The highest rates were for patients without insurance coverage, classified as self payors (24% by both tests). By the b-MAST, 25% of workmen's compensation cases were alcoholics. Low rates were found for the Medicare (5% b-MAST, 6% CAGE) and Blue Cross interviewees (3% and 5%).

As expected, the prevalence rates of alcoholism were significantly higher for those patients who admitted to drinking alcohol, 11% and 14% by the b-MAST and CAGE, respectively. The b-MAST determined that 2% of the patients denying any alcohol use may have actually been alcoholic. Patients who had smoked at any time had a significantly higher prevalence rate of alcoholism by both questionnaires than patients who had never smoked. Interviewees with a history of illicit drug use also had a significantly higher prevalence rate of alcoholism by both screening tools (22%) than those with no history of drug use. Thirty percent of patients with a his-

TABLE 4
Alcoholism Prevalence Rates in Risk Groups

	Prevalence %		p Value	
	b-MAST	CAGE	b-MAST	CAGE
Sex				
Male	13	15	0.003	0.0005
Female	4	5		
Patient type				
Service	14	13	0.006	0.09
Private	5	7		
Patient type by sex				
Male service	25	21	0.02	0.3
private	9	13		
Female service	8	8	0.06	0.1
private	3	3		
Insurance type				
Self pay	24	24	0.002	0.03
Workmen's compensation	25	13		
Private insurance	10	13		
Medicaid	8	9		
Medicare	5	6		
Blue Cross	3	5		
Alcohol history				
Yes	11	14	0.002	0.0001
No	2	0		
Smoking history				
Yes	14	13	0.0001	0.002
No	1	4		
Illicit drug history				
Yes	22	22	0.0001	0.0001
No	4	6		
Heroin	30	30		
Methadone	17	17		

tory of heroin use and 17% of those in methadone maintenance were alcoholic by both tests.

Other parameters examined were occupation, admission type, race, service, education, and number of people in room at time of interview. There was no significant difference in prevalence rate for any of these categories.

Prevalence rates grouped by interviewer were found to be different, though not significantly. One interviewer's cases had a reduced prevalence of 1% by b-MAST and 2% by CAGE. However, the parameters associated with significantly higher prevalence rates of alcoholism (sex, patient type, insurance, and alcohol and smoking history) were distributed unevenly between the cases studied by each interviewer. The dissimilar alcoholism prevalence rates of the 4 interviewer groups of cases was most likely due to difference in the demographics of the groups themselves.

Discussion

The prevalence rate of alcoholism in this study population was estimated to be 7% by the b-MAST and 8% by the CAGE questionnaire. When one screens the whole spectrum of patients in acute care in a general hospital, including the numerous services, private and nonprivate patients, various races, ethnicities, and ages, and all severities of illness, the prevalence rate of alcoholism is lower than that suggested by the literature. In fact, the prevalence rate of 7% to 8% is similar to that of the United States population (1, 2). The acute-care general hospital patient population does not appear to be at high risk for alcoholism as a whole.

High Risk Groups. Groups with significantly higher rates of alcoholism included males, service patients, and patients without insurance. In fact, 21% to 25% of male service patients were found to be possible alcoholics. Other subsets at high risk for alcoholism were those patients who admitted to drinking alcohol, smoking, and using illicit drugs. Both screening tools consistently found the same groups to be at high risk. The lowest prevalence rates of alcoholism were found among females, Medicare and Blue Cross patients, nondrinkers, and nonsmokers (Table 4).

Comparison with the Literature. The prevalence rates of alcoholism yielded by prior studies were found to be in the same range as for corresponding subgroups of patients in this study. Studies in Veterans Administration hospitals yielded prevalence rates of 12% to 55% (4, 5, 14–16), which corresponded to the prevalence rate of 25% by the b-MAST of the male service patients at Beth Israel Hospital. The prevalence rate in city hospitals ranged from 32% to 47% (17, 18), possibly corresponding to this study's patients without insurance (24% percent, by both tests). Studies at community hospitals yielded prevalence rates of 9% to 16%, male rates being greater than female rates (3, 19, 20). Community hospitals, with their broader spectrum of patients, had lower prevalence rates of alcoholism than those of the Veterans Administration, city, and military hospitals, consistent with the determination in this study of a prevalence rate of 7% to 8%. This study population encompassed an even broader representation of patients of an acute care hospital than that of the previous studies at community hospitals (6).

Many reported studies were undertaken at Veterans Administration and city hospitals and focused on service patients on medical and surgical services; female patients were often not included. Most of these studies screened subgroups of the acute-care general hospital population that were found to be at high risk in this study. This study population encompassed private as well as service patients of all degrees of illness and all services, including a large obstetrics and gynecology service, which increased the proportion of females. As well, a large percentage of cases had either Blue Cross or Medicare coverage.

The Tests. The two questionnaires both yielded similar prevalence rates of alcoholism. Though some of the alcoholic cases detected by the two tests were different, both questionnaires were found to be reliable, with statistically significant agreement in their classification of cases as alcoholic or nonalcoholic. The degree of agreement between these screening tools had not been measured previously. Since the reliability was good, use of either of the tools would yield similar information.

The prevalence rates yielded by this study were limited by the extent of the validity of the screening tools utilized. Both questionnaires were validated in the literature in limited populations and were found to have excellent sensitivities and specificities in their original validation studies (11, 12). A more recent community study found the CAGE questionnaire to be twice as sensitive as the b-MAST. However, neither test picked up more than 50% of the known alcoholics (22). Given the variability in defining the criteria of alcoholism and the difficulty of accurately validating alcoholism, the true validity of these tools is not certain (7). Nor was current versus prior status of alcoholism established (23).

The literature suggests that interview screening techniques for alcoholism are limited by the patient's awareness of drinking as a problem (9, 22). This may be true for less than one half of alcoholics (22). Since these tests focus on social and behavioral manifestations of alcoholism, they may miss those patients with resultant physical disease who are regarded as social drinkers (24).

In order to further evaluate the validity of the b-MAST and CAGE in this study, one would have to use another effective measure to identify the alcoholics and to see how many true alcoholics were detected by either screening tool. Though their validity is less than that originally calculated, these tools are the most frequently used to date, and are easy to administer. Many of the previous studies used screening tools which had not been previously validated in the literature (6).

Limitations. Because a broader cross-section of randomly selected patients was screened and two tools previously validated in the literature were used, the alcoholism prevalence rate determined in this study is believed to be more representative of that of other acute-care general hospital patient populations than rates generated in prior studies. The demographic characteristics of the patients interviewed and not interviewed were similar, including those characteristics associated with significantly different alcoholism prevalence rates.

Several limitations should be discussed. Although 75% of the patients selected were interviewed, 12% had too short a hospital stay to be contacted in time for an interview or to obtain permission from the private attending. It is unclear whether this group is more or less likely to be alcoholic. Prior studies have shown that patients with underlying alcoholism tended to have a longer hospitalization for their primary illness (25). Either the patient or the attending physician refused permission to interview in 7%; alcoholics may refuse to participate in such a study, or their private physician may try to protect them from the study. However, the true purpose of the study was not revealed to them. Two percent of patients signed out against medical advice soon after their arrival in the hospital. These may have been more volatile individuals such as alcoholics who left the hospital in order to resume drinking (Table 1).

It is unclear whether the affiliation of Beth Israel Hospital with Bernstein Institute, a major drug and alcoholism rehabilitation treatment center, would increase or decrease the rate of alcoholism. All patients who are admitted for alcoholism or illicit-drug detoxification or for an associated medical illness would enter Bernstein Institute. However, if the patients have other medical or surgical problems, they would be admitted to Beth Israel Hospital. It would be important to ascertain whether the prevalence rates of illicit drug use in Beth Israel Hospital determined by this study are similar to rates of other acute-care general hospitals.

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Error Rate Factor in the Management of Suspected Acute Appendicitis: Has Anything Changed?

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Abstract

Physician motivation has been shown to play a key role in accurate diagnosis of acute appendicitis. I attempted to find and explain differences in such accuracy over time and between private attendings and house staff of a large urban teaching hospital. Retrospective chart review of 74 appendectomies performed at The Mount Sinai Hospital in 1973 (n, 34) and 1981 (n, 40) showed decrease in rate of removal of normal organs from 21% in 1973 to 8% in 1981. Frequency of perforation simultaneously declined from 41% to 30%. Removal of normal organ and perforations were fewer in the clinic population than the private in both years. It is concluded that the increase in accuracy of clinical diagnosis was not due to changes in patient characteristics, diagnostic techniques, or indications for surgery, but rather to increased attentiveness by physicians to known predictors. Clinic patients benefitted most, suggesting that house staff are influenced more by social, political, and economic motivators than private attendings. Further reductions in diagnostic error rates can be achieved by improving diagnostic acumen and have great implications for savings in number of operations and convalescent days, mortality, and health care expenditures.

The diagnosis of acute appendicitis has plagued physicians for centuries and continues to be a frequent dilemma for practicing surgeons. In 1955 Cantrell and Stafford stated: "A figure of 20 to 25 percent normal appendices in patients with the preoperative diagnosis of acute appendicitis should not be looked upon as an unreasonable figure, but as a necessary evil" (1). Since then, many studies consistently show diagnostic accuracies of 67% to 80% for acute appendicitis, confirming that a surprising number of aspects of the diagnosis and treatment of this "simple" condition remain inadequately defined and poorly understood (2).

Is this disease an enigma for the medical professor, or are physicians more interested in newer, more complex challenges, at the expense of basic clinical medicine? These questions were addressed by several studies in the mid to late 1970s, a period critical to the history of appendicitis. During this time, short-term prospective studies demonstrated that improvements in accurate diagnosis of acute appendicitis were possible thus disproving traditional beliefs (3, 4).

The goals of the present study were as follows. First, to perform a study similar to the previous ones in the new setting of a large urban teaching hospital. Second, to determine whether improvements in diagnostic accuracy reported in these short-term prospective studies might occur over a long-term interval, specifically the period of the discoveries of the mid-to-late 70s. Third, to evaluate possible factors associated with any long-term changes found, including changes in patient characteristics, diagnostic technologies, indications for surgery, physician motivation. Fourth, to detect any differences in the performance of house staff versus private attendings as measured by normal removal and perforation rates.

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Review of Literature

Incidence and Pathogenesis. First identified by Fitz in 1886 as a clinical and pathologic entity requiring surgery, appendicitis is currently the most common acute surgical condition of the abdomen (5, 6). The disease occurs at all ages, but is most frequent in the second and third decades. The sex ratio is about 1:1 before puberty; at puberty the male-to-female ratio increases to about 2:1, and after age 25 the male incidence gradually declines.

The incidence of acute appendicitis requiring appendectomy has dropped significantly over the past three to four decades, and the trend appears to be continuing. Currently, 200,000 appendectomies for acute appendicitis are performed annually in the United States. No reason for the decline has been established, but speculation suggests changes in dietary habits and intestinal flora, better nutrition, higher vitamin intake, and antibiotics.

The pathogenesis of acute appendicitis involves bacterial infection distal to obstruction of the lumen. The blood supply is gradually impaired by luminal distention and intramural edema; gangrene and perforation occur at about 24 hours.

Pitfalls in Diagnosis. The diagnosis and management of an acute abdomen is a subject of controversy among physicians. Definitions of acute abdomen vary from the radical view, "an acute condition within the abdomen demanding immediate operation" to the more conservative "abdomen that requires an acute decision" (7). Few would disagree however, that the acute abdomen is a condition stressful for both patient and physician.

Many authors attribute the difficulty in diagnosis of acute appendicitis to the great variability in position of the offending part which leads to wide variation in symptoms and histories. DeDombal, however, claims that in the majority of cases, the incorrect diagnosis of appendicitis results from careless history taking, interviewing, and physical examination of the patient (3).

While the young healthy male patient is usually not subject to these errors in diagnostic judgment, continued efforts are needed to improve diagnostic accuracy in the pediatric and geriatric age groups and in females of reproductive age. The difficulties inherent in obtaining an accurate history from and in examining the child are reflected by increases in the average duration of symptoms, perforation rate, morbidity, and mortality for appendicitis among children (8, 9).

The fact that older persons may have difficulty in giving a reliable history, tend to delay seeking medical attention, and often suffer from systemic illnesses contribute to the problem that surgeons face in establishing a diagnosis of appendicitis in the elderly patient. Perforation with resultant excessive morbidity is thus the rule rather than the exception among the aged (10).

The ovulating female, however, presents the greatest diagnostic challenge to the physicians.

Dunn's review of appendectomies reveals, for women aged 13 to 40, error rates of up to 35% (11); other studies report that up to 50% of young females who undergo appendectomy have normal appendices removed (12). Gynecologic disorders (especially pelvic inflammatory disease, or PID, and mesenteric adenitis) are the most common findings at laparotomy. The recent marked increases in the incidence of PID and subsequent ecotopic pregnancies promise to create increasing confusion in establishing the proper diagnosis in this group of women.

Improving Diagnostic Techniques. For the practicing surgeon, physical examination of the acute abdomen is routine. Signs to be elicited in the differential diagnosis of appendicitis are classic, well known, and easily interpreted. Techniques for clinical diagnosis have not changed over the years, and will not be discussed in detail, but one cannot overemphasize the value of a careful physical exam by a vigilant physician.

Unlike the clinical examination, diagnostic technology is a rapidly expanding field of great potential benefit for physicians and patients. The roentgen exam (13, 14), ultrasound (15, 16), barium enema (11, 17), and laparoscopy (7, 18, 19) have all been used in differential diagnosis; recent reevaluations have shown each to be of value in the situation of acute abdomen suggestive of appendicitis. In the past, suggestions for a more thorough preoperative assessment have been opposed on the basis of cost. Although a more extensive evaluation usually translates into a more expensive one, the information gained can be invaluable and cost effective.

Indications for Appendectomy—Medical Decision Making. In the face of this uncertainty, surgeons traditionally have argued the benefits of a noninterventional versus an interventionist approach, assuming an inevitable trade-off between deaths resulting from complications of too many appendectomies and those resulting from delayed treatment of perforated appendices (2). Yet few consider the basic problem of how to improve decision making. In the mid-to-late 70s, however, four authors were major pioneers in this field, building a new philosophy supported by surgical experience and theoretical decision analysis.

DeDombal (1974) performed a controlled trial of human and computer diagnosis in patients with acute abdominal pain (3). Prior to the experiment, the diagnostic performance of the surgical service was a true positive rate of 60% (40% of appendices perforated at operation); 25% of normals received an operation (false positives). During the six-month experiment, surgeons filled out a precoded form for symptoms, data from which was fed into a computer for "real time" diagnosis. Although the diagnosis was not available to the clinicians, they were well aware of their rival; they were motivated to compete with the computer and their performance improved markedly: 96% true positives and 7% false positives were found. Six months after the trial was over, their rates of performance reverted to preexperimental values.

Since neither the staff nor the patients' characteristics had changed, the author was not sure what he should attribute these changes to. Changes in motivation and the data base (due to the precoded form) were two possible factors mentioned. Whatever the precipitating factor, the important finding was that competition resulted in a simultaneous reduction of false positives and perforations (previously accepted as impossible).

White (1975) reported a similar experience at Johns Hopkins (4). The original performance resulted in 65% false positives and 74% true positives. After a new policy of improved patient workup with intensive in-hospital observation for questionable cases was instituted, accuracy improved 14% and the incidence of negative laparotomies declined 13%; true positives were stable and false positives dropped.

The third and major contribution to the new stance came from Neutra's work of 1977 and 1978 (20, 21). Using theoretical models together with the surgical experiences of deDombal and White, he developed three arguments against traditional beliefs:

First, using symptom severity distribution curves, he pointed out that traditional arguments "overlook the fact that the adequacy of the patient workup affects the ability of a symptom severity score to separate cases of appendicitis from cases of nonspecific abdominal pain." Consequently, improved patient workup can dramatically increase discrimination.

Second, he introduced the Receiver Operating Characteristic (ROC), a graph of true versus false positives, as an analytic tool. Applying it to appendectomy, he defined the true positive rate as the percentage of appendicitis patients who receive a timely operation. The false positives correspond to the percentage of normal patients who are operated upon (Fig. 1).

Finally, he conducted an extensive analysis of cost effectiveness in treating appendicitis, concluding that

> changes in the degree of discrimination can have important implications in terms of lives saved, dollars spent, and convalescent days experienced. If White's points are extrapolated to the U.S. population, yearly savings of great magnitude can be achieved. There is a difference of 259,000 operations. . . . Fewer operations on normal persons would reduce deaths by 169 but would reduce convalescence by about 6 million days. Hospital costs would decrease by more than a third of a billion dollars, enough to provide $687 to each of the 541,475 patients operated on under the unusually interventionist strategy. . . . more than enough to pay for the additional services of a doctor and/or nurse to observe these patients in the emergency ward for 6 to 12 hrs.

Overuse of Surgical Services. Rates of appendectomy and other common surgical procedures have been used as barometers of surgical care in several studies. For example, Lembcke studied the incidence of appendectomy in 23 hospital areas in and around Rochester, NY in 1969 (22), and inferred "that in areas served by hospitals

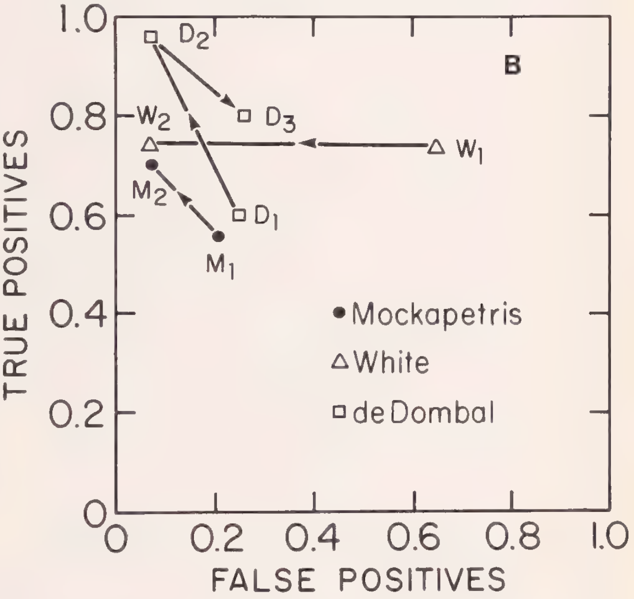

Fig. 1. Receiver Operating Characteristic graph of true positives and false positives for appendectomy. White's experience (W_1, W_2) suggests that improved discrimination allows decrease in rate of removal of normal organs without increasing perforations. Experience of deDombal (D_1, D_2, D_3) suggests that perforation rates and normal-organs removal rates can be simultaneously reduced. In present study (M_1, MSMC 1973; M_2, MSMC 1981), "false positive" rate is defined as percent of appendectomies found to have normal pathology, or normal removals/all removals (traditional "normal removal rate" in surgical literature). DeDombal (3) and White (4) define "false positive" as percent of normal patients operated on or normal removals/nonspecific abdominal pain.

where operations are not strictly controlled, the simple fact of greater accessibility to medical care is a deciding factor."

Lewis examined records of the Kansas Blue Cross Association for 1965 (23) and found a threefold to fourfold variation in rates not only for elective operations such as tonsillectomy, but also for procedures assumed to have more definitive indications, such as appendectomy. Using regression analyses, Lewis concluded "that patient admissions for surgery expand to fill beds, operating suites and surgeons' time."

A 1982 study by Wennberg examines variations in surgical rates in small areas in New England (24). Of previous studies, he says: "The wide variations in the rates of individual procedures, however, are not caused by differences in the supply of resources alone. Our work suggests that such variations are due to differences in the style of medical practice of local physicians." Wennberg proposes that the clinical judgment of physicians within a region (and hence the rates of surgical procedures) constitute a "surgical signature" for that area that tends to be consistent over many years unless physicians enter or leave.

The alleged overuse of surgical services in this country is often attributed to lack of consumer knowledge. To test this hypothesis, Bunker examined the behavior of physicians as well-informed patient and compared their use of surgical services with national rates and with three other professional groups of equal education and affluence (lawyers, ministers, business people) (25). He found that the amount of surgical care received by physicians and their spouses is as high as or higher than that for other professionals, and on the average, higher than in the country as a whole. For appendectomy, the rate among physicians was twice the national rate from age 25 to 40, when medical education has presumably been completed. The study failed to ask whether the difference was due to increased demand by the informed physician-patients or the increased supply of services available to them. Nevertheless, the conclusion was that "the physician-patient as an informed consumer places a high value on surgical care . . . and as the public becomes more fully informed, the demand for surgical services will increase."

In summary, physicians currently place a high value on the strategy of removing suspected appendices in their patients, their families, and themselves. Judging from recent data, appendectomy rates may well exceed the point of positive benefit-to-risk ratio. These studies imply that much of the unnecessary surgery is the result of financial incentives of enterprising surgeons, rather than benign misjudgment, and have important implications for policy makers. Controversies do exist, however, and have evoked passionate, opposing views, highlighting the enormous uncertainty about the appropriate application of surgery. Certainly, further investigations into these issues are strongly indicated if the public good is to be served.

Methods

Appendectomy cases of The Mount Sinai Medical Center (MSMC) were targets for this study. MSMC is a 1,200-bed tertiary care teaching facility in New York City. MSMC appendectomy patients, however, differ from this general population first because health emergencies such as the acute abdomen limit hospital catchment areas. In this study, 60% of the patients claimed residence in New York City; the remainder were from surrounding suburbs of New York and New Jersey. Second, the majority of patients had not been seen by any physician prior to appearing in the emergency room. Only 7% had sought medical care as outpatients; all but one of this group were immediately referred to MSMC for admission.

This is a retrospective case study of appendectomy patients treated at MSMC in 1973 and 1981, representing years before and after the revisions proposed in the mid to late 70s by deDombal, White, Neutra, and Bunker, in the hope of capturing a comparison of the "state of the art" for these two years. Of the first 50 appendectomies performed between January 1 and May 17, 1973, 42 met the criteria of available and complete patient records, operative summaries, and pathology reports. Eight interval appendectomies were excluded, providing a total of 34 cases for analysis. Of the first 50 appendectomies performed between January 1 and April 28, 1982, 43 were complete; 3 interval appendectomies were excluded, for a total of 40 cases to be studied.

Demographic variables extracted were age, sex, status as private or clinic patient, location of residence. Historical data included first visit, referral, previous visits for abdominal pain, hospital admission date and time, operation date and time, admitting diagnosis, and discharge diagnosis and date. Also extracted from case files were symptoms and signs in detail; laboratory tests including CBC with differential, sedimentation rate, and urine analysis; any diagnostic test results; surgical opinion by operative and discharge note, and pathology reports; length of stay and any postoperative complications and their treatment.

Analysis of this data proceeded as follows: First, case rates by condition of removed appendix (normal, acutely inflamed, perforated) were calculated. Second, discriminant analysis using the Statistical Package for Social Science (SPSS) was performed in attempt to differentiate the groups on the basis of several independent variables. The preoperative characteristics which had the best predictive value were thus determined for each year. The third stage of the study asked whether the results of the first two parts had changed with time from 1973 to 1981, and if so, why? Had patient characteristics changed? Were new diagnostic techniques being used? Had the general indications for surgery changed (as measured by the discriminating variables)? Or had social, political, or economic pressures created incentives for physicians to change their behavior?

The major methodologic limitation to be noted is the absence of a cohort control group; those patients with abdominal pain suggestive of appendicitis who did not undergo appendectomy were missing from the study. These cases correspond to the false negatives and true negatives with regard to the physician decision to operate for suspected acute appendicitis. Attempts to evaluate physician performance in clinical decisions without these cases is recognized as unfair and improper. This limitation was impossible to avoid. Files of patients with abdominal pain upon whom physicians chose not to operate are scattered among a multitude of discharge diagnoses. Listings of such patients are impossible to obtain, unless review of all emergency room cases of abdominal pain is done. Practical considerations prohibited this.

Fortunately, this flaw in design had little effect on the major issue of this study: the change in outcome of appendectomies between 1973 and 1981, and an explanation thereof. The study design focused directly on this issue, and allowed the pertinent questions to be answered.

Results

Descriptive Statistics. *Demographics:* The distribution of appendectomy cases by age, sex, and status as private or clinic patient (Table 1) revealed no significant differences between these groups and prior reports.

Accuracy in Diagnosis: Diagnostic accuracy is defined here as the percentage of removed appendices which were actually inflamed (as confirmed by pathology report), or the sum of acutely inflamed and perforated appendices divided by the total cases. Overall accuracy and subgroup rates appear in Table 2.

TABLE 1

Demographic Characteristics, Appendectomy Cases

	1973 n = 34	1981 n = 40
No. females	15 (44.1%)	23 (57.5%)
No. males	19 (55.9%)	17 (42.5%)
Age range	6–82	3–75
No. under 10 years	7 (20.6%)	5 (12.5%)
No. over 50 years	4 (11.8%)	7 (17.5%)
25th percentile age	11	14
50th percentile age	28	22
75th percentile age	41	38
90th percentile age	52	53
Mean age ± SD	28.9 ± 19.1	27.8 ± 19.5
No. private pts	15 (44.1%)	24 (60.0%)
No. clinic pts	19 (55.9%)	16 (40.0%)

Removal of Normal Organs: In 1973, 7 cases (20.6%) were found in which the primary diagnosis of appendicitis was false; of these, 3 had other surgical diseases (perforated diverticulum, bowel infarction), and 4 were found to have nonsurgical disease (PID/salpingitis, acute ileitis, nonspecific abdominal pain). In 1981, only 3 normal appendices were removed; for all of these patients, nonsurgical diagnosis was made at laparotomy.

Perforation Rates: In calculating incidence of perforated appendices among all appendectomy cases, overall and for various subgroups (Table 3), one case with rupture of a diseased appendix due to the surgical maneuver was not included.

Discriminant Analysis. Discriminant analysis of the 1973 cases grouped as normal, acute, or perforate was performed to determine the patient characteristics which could best predict the condition of the removed appendix. Discriminating variables were age, sex, private or clinic status,

TABLE 2

Diagnostic Accuracy by Sex, Age, and Private-Clinic Status

Accuracy	1973	1984
Overall	79.4%	92.5%
Among females	66.7	86.7
Among males	89.5	100.0
Under 10 years	85.7	100.0
Age 11–50	78.3	97.4
Over 50 years	75.0	71.4
Among private pts	80.0	88.0
Among clinic pts	80.0	100.0
Poorest	62.5 (♀ 21–40)	71.4 (♀ over 50)

TABLE 3

Incidence in Percentage of Perforated Appendix Removal

Perforations	1973	1981
Overall	32.4	27.5
Among females	20.0	21.7
Among males	42.1	35.3
Under 10 years	57.1	60.0
Over 50 years	75.0	14.3
Private pts.	50.0	31.8
Clinic pts.	40.0	35.0
Among proven cases of appendicitis	44.4	29.7

duration of symptoms, fever, nausea, vomiting, diarrhea, location of pain at onset (epigastric, diffuse, or right lower quadrant—RLQ), migration of pain to RLQ, bowel sounds (normal, increased, decreased), location of tenderness on physical exam (epigastric, diffuse, RLQ), rebound, guarding, rectal tenderness, pulse, temperature, and white cell count.

The ten best predictors of the condition of the removed organ as determined by discriminant analysis for the 1973 cases are listed in Table 4 in order of decreasing importance (discriminant coefficient). The combination of these variables with their respective coefficients in the discriminant equations could correctly predict the final diagnosis in 94% of the 1973 cases. By classification of ungrouped 1981 cases using the 1973 equations, accuracy dropped to 78%.

Analysis using the 1981 grouped cases determined the best predictors for 1981 cases (Table 4). Seven of the ten best predictors were the same for both years. The 1981 equations could correctly classify 90% of the 1981 cases.

Discussion

Improvement in Accuracy. Results from the two sampling points, 1973 and 1981, indicate significant improvements in diagnostic accuracy as measured by various rates of performance. Surgeons at MSMC were found to have improved their overall accuracy rate for the diagnosis of acute appendicitis requiring surgery by 13%; in 1973, 79% of all removed appendices were acutely inflamed or perforated, whereas in 1981 this rate increased to 92%. In other words, the normal removal (or false positive) rate decreased from 21% to 8% ($\chi^2 = 2.7, p < 0.1$). True positives, defined as acutely inflamed appendices removed prior to perforation (timely removals), increased from 55.6% in 1973 to 70.3% in 1981, and perforations fell from 44.4% to 29.7% ($\chi^2 = 1.4, p < 0.3$).

Fig. 1 shows the Receiver Operating Characteristic (ROC) plot of this data, and the data of deDombal and White. The definition of false positives in this study, a result of the exclusion of patients not operated on, differs from the definition in the other two studies. This discrepancy prohibits comparison of precise rates, but movement is certainly in the same direction. Thus, the current study results add further support to the contemporary belief that removals of normal organs and perforations can be simultaneously reduced.

A significant difference between the studies is the time elapsed between sampling points. The studies of deDombal and White demonstrated that significant improvement could occur over a short period (as little as 6 months), but unfortunately, regressions could happen just as rapidly. This study compares accuracy at the beginning and end of an eight-year interval, demonstrating that improvement is possible over a longer period. It is to be hoped that these results represent a slower, more stable improvement and a general trend which will not revert to prior levels as in the previous studies. However, more sampling points are required to justify the notion that these isolated points in time do indeed represent a trend, and not merely random fluctuation.

Why the Improvement? Possible explanations for the observed improvement included changes in the characteristics of the patients or their illness, increases in the use of diagnostic technologies, differences in the accepted indications for appendectomy, replacements in staff, and as deDombal had suggested, improvement in physician motivation to perform accurately. Each of these possibilities was investigated.

Demographic Variables: Patient distribution by sex showed no significant change (Table 1); for women, $\chi^2 = 1.3, p > 0.2$. Age distribution was also similar. Range, mean, and median values of age showed no significant change (largest $t = 0.23, p > 0.7$). In 1973, 44.1% of patients were private and treated by private attendings, compared to 60.0% in 1981 ($\chi^2 = 1.4, p > 0.2$).

Symptomatology: The distribution of the duration of symptoms prior to operation showed no significant change from 1973 to 1981 ($t = 1.1, p > 0.2$). No significant change between 1973 and 1981 was found in the incidence of any of the symptoms for which incidences were calculated (fever chills, anorexia, nausea, vomiting, diarrhea, constipation, location of pain at onset, and migration of pain to RLQ).

Clinical Findings: The subjective findings on physical examination that were investigated were character of bowel sounds, location of maximal abdominal tenderness, rebound, guarding, rectal tenderness, pelvic tenderness among females, and presence of a mass felt through abdominal wall. Only one change was noted: a decrease in incidence of pelvic tenderness among female patients, from 33.3% in 1973 to only 8.7% in 1981 ($\chi^2 = 3.68, p < 0.1$). The significance of this change is difficult to evaluate for two reasons: (a) the small sample size of female patients, and (b) the difficulty in determining whether this change was due to actual changes in patient characteristics or to changes in the care which physicians used in performing pelvic examinations. Diagnostic accuracy was known to be poorest in young females of reproductive age; perhaps this change in incidence of pelvic tenderness represents the result of increased physician awareness of diagnostic confusion in this group and the importance of a careful physical examination.

The distribution of pulse, temperature, and white blood cell count, which might be considered more objective clinical findings, was different for the two years. Pulse rate was below 100 in 70.5% of the 1973 cases, and in 87.5% of the 1981 cases ($\chi^2 = 3.3, 0.05 < p < 0.1$). A corresponding change in temperatures was noted; in 1973, 52.9% of patients had preoperative fevers below 101°F, whereas 85.0% of the 1981 cases had such low-grade fevers ($\chi^2 = 9.03, p < 0.01$). The change in white blood cell values was less dramatic: 64.7% of the earlier cases and only 47.5% of the later cases had counts below 15,000 ($\chi^2 = 2.2, p < 0.2$).

Diagnostic Tests: A slight but nonsignificant increase in the use of diagnostic techniques was noted. In 1973, 70.6% of all patients had abdominal x-rays, compared to 77.5% in 1981 ($\chi^2 = 0.5, p = 0.5$). Barium enema and sonogram were not used in 1973 but were used in three cases each in 1981. Laparoscopy also was not used in the 1973 cases, and was used only once in 1981 to identify a perforate appendix.

In sum, demographic variables, symptomatology, most clinical findings, and the use of diagnostic techniques were not significantly different in the two years studied. The incidence of pelvic tenderness, elevated pulses, fevers, and high white blood cell count had changed. However, these results are biased by the exclusion from this study of patients not undergoing operation. It is thus difficult to judge whether these changes were a result of the patient population itself or merely a reflection of physicians' selection of patients who underwent appendectomy.

Indications for Appendectomy: No definition of absolute indications for appendectomy exist; these rules are unwritten and vary. To evaluate the contribution of this variable to the improvement in accuracy, the indirect method of discriminant analysis was used. The discriminant equations derived may be considered to represent the optimal set of rules for deciding when to operate for suspected acute appendicitis.

Seven of the ten best predictors did not change from 1973 to 1981 (Table 4). It is not unreasonable to infer that while most of the accepted indications for appendectomy had not changed, minor modifications had been incorporated into these "rules." This new ranking could result in slight improvements in diagnostic accuracy.

A summary of the accuracies resulting from human and computer-generated (discriminant analysis) diagnosis (Table 5) verifies that a most gratifying improvement in accuracy occurred. In 1973, physicians at MSMC performed at a level (79% accurate) similar to other reported centers (2), yet significantly below the optimal accuracy suggested by discriminant analysis (94%). In 1981, however, the human diagnosticians had improved markedly; their accuracy of 92% was well above reports from most centers, and—even more surprisingly—was above the optimal accuracy of computer diagnosis by discriminant analysis (90%).

Improvements such as these must be commended, and physicians encouraged to continue their efforts. One can only hope that these results reflect the general status of this problem, and not an isolated success story in clinical decision making.

Private Attendings vs. House Staff: The data on accuracy and perforation rates for private versus clinic patients is worthy of much consideration (Tables 2, 3). House staff who treated clinic patients were much more successful than private attendings in accurately diagnosing appendicitis in number of normal organs removed and of per-

TABLE 4

Best Predictors by Discriminant Analysis

Rank	1973	1981
1	Pulse	Nausea/vomiting
2	Rebound/guarding	Duration of symptoms
3	Rectal tenderness	Rebound/guarding
4	Temperature	Temperature
5	Sex	WBC count
6	Location of tenderness	Sex
7	Age	Location of tenderness
8	Diarrhea	Location of pain at onset
9	WBC Count	Migration of pain to RLQ
10	Nausea/vomiting	Pulse

TABLE 5

Human and Computer-Generated Diagnostic Accuracy

	1973	1981
Human accuracy	79.4%	92.5%
Computer accuracy by discriminant analysis		
1973 predictors	94.1%	78.0%
1981 predictors		90.0%

forations. Implications are that private surgeons had less incentive to accurately diagnose, perhaps due to less external pressure to perform and more negative financial incentives than house staff.

Summary

It is concluded that between 1973 and 1981 physicians at MSMC became increasingly aware of their error rate in the diagnosis of appendicitis as a result of the various controversial studies of the mid to late 1970s. They were motivated to change their behavior in the hope of improving accuracy. Diagnostic acumen was increased, and minor modifications in the indications for surgery adopted, the result being improvement in clinical diagnosis of acute appendicitis. Clinic patients had lower rates of removal of normal organs and perforations than private patients, indicating that the motivating factors for improvement had more impact on house staff than on private physicians.

A model to explain the impact of technology assessment on clinical practice has been proposed by Finkelstein and Temin (26). A twofold mechanism is described: first, people become aware of the existence of a recommendation; second, they are persuaded to follow it. Awareness is a key component of the model. Physicians tend to act according to what Temin calls the "customary" mode of behavior, which reflects what physicians consider to be the norms of their profession. If they become aware of a discrepancy between their behavior and scientific evidence, they can shift from customary behavior to "instrumental" behavior, in which they reexamine their behavior and seek to conform to the new evidence.

This model describes what is proposed to have happened in the case of appendicitis, namely, that publicized assessment of the surgical procedure induced behavioral changes among informed surgeons. Although Temin's evidence suggests that new information has a greater impact on behavior than a reanalysis of existing data, the present study demonstrates that innovative reappraisals of old problems can be of benefit to physicians and their patients.

Suggestions for further study include:

1. Repetition of the present study using the population of all patients who enter the emergency room complaining of lower abdominal pain, in an effort to include those cases not operated on.
2. Repetition of the present study at additional points in time to determine the progression of accuracy and perforation rates over time.
3. A prospective study to follow the accuracy rates of house staff as they progress in their careers to become private attendings. Such a study might reveal information regarding incentives to operate.
4. Use of this study as a prototype for evaluations of other "questionable" surgical procedures such as hysterectomy, hernia repairs, hemorrhoidectomies, cholecystectomies, varicose-vein operations.

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Refusal of Treatment: The Role of Psychiatric Consultation

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The issue of refusal of treatment and tests has implications that range from minor disruptions of hospital procedure to profound legal and ethical dilemmas that concern individual rights and the quality of life. Refusals of tests and treatment are commonplace events in medical practice (1). Appelbaum and Roth estimate that an average of 18 refusals occur each day in hospital (1). In their longitudinal study of treatment refusal in medical hospitals, 0.7–11.4 refusals per 100 patient days were observed, the highest rates occurring in university teaching hospitals. The procedures or treatments refused were equally divided among medications, diagnostic procedures, and adjunctive care. The definition of "refusal" used by Appelbaum and Roth ranged from refusal to consent to necessary procedures in emergencies to patient noncompliance with bed restrictions and daily weighings.

The act of refusal of tests and treatment can be viewed as a form of noncompliance. Noncompliance has been defined as "an inability or abject refusal on the part of the patient (for conscious or unconscious reasons) to comply with the medical regimen presented by his physician, or to continue in treatment" (2). Refusal is a manifestation of noncompliant behavior in which a specific recommendation is explicity rejected. Whereas noncompliance includes such behavior as inability to adhere to medication schedules or restrictions or to appear for follow-up visits, "refusal" connotes a direct, independent interruption of medical care. When psychological features reach pathological proportions, the question of competence to refuse (or consent to) treatment becomes an important issue.

In the present study, the issue of treatment refusal was explored through an assessment of those cases in which it was cited as the reason for requesting a psychiatric consultation. (From the consultee's point of view, it is likely that the medical consequences of treatment refusal were quite serious, or alternatively, that the doctor-patient stalemate incurred by the refusal made it difficult to continue a therapeutic plan.) Admittedly, this comprises a small and select subgroup of refusers. The examination of the psychiatric evaluation of those patients who refuse treatment in a hospital offers a unique opportunity to probe the problem of refusal.

Methods

A computerized form recording the findings of the psychiatric consultation process was used. The database includes demographic information; patient consultee data; reasons for consultation as stated by medical consultee and as assessed by consultant; DSM III diagnosis, Axis I–V; as well as recommendations for treatment.

The degree to which the medical consultee and the psychiatric consultant concur or disagree on the initiating problems reveals in part the ability of the nonpsychiatric physician to detect specific psychiatric morbidity. Therefore, the reasons for consultation other than the refusal itself stated by the medical consultee were compared with all reasons as assessed by the psychiatrist. Finally, DSM III diagnostic criteria were employed as the psychiatrist's assessment of the patient.

All cases were evaluated by postgraduate year 3 psychiatric residents under the supervision of senior faculty of the Consultation/Liaison Division. Each consultation form was reviewed and

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over one-half of the patients were seen by supervisors to ensure the reliability of the data.

From 812 consultations over a three-year period at The Mount Sinai Hospital, 97 patients (11.9%) were identified as "refusers," that is, the refusal of tests or treatment was among the stated or assessed reason for consultation. Refusers were compared to "nonrefusers," patients whose consultations were initiated for reasons other than a stated or assessed refusal of tests or treatment.

Results

Refusers vs. Nonrefusers. Refusers could not be differentiated from nonrefusers on a demographic basis; there were no significant differences with respect to sex, age, employment, marital status, or living situation. Furthermore, no distinctions could be made on the basis of medical diagnosis (Axis III) or previous history of psychiatric illness.

However, when reasons for consultation as assessed by the psychiatrist were considered, several key differences emerged (Table 1). Refusers as compared to nonrefusers were assessed as significantly more noncompliant; more frequently behavior management problems; and having a higher incidence of impaired judgment. Organic brain syndrome and problems in coping with chronic illness were cited as reasons for consultation by the psychiatrist more often in the refusers than the nonrefusers, whereas suicidal tendency and depression were less. Refusers were more likely than nonrefusers to evoke an emergency consultation and have greater severity of psychiatric illness and psychosocial stress.

Administrative action was taken ten times more frequently for refusers categorized as "impaired judgment" and "discharge against medical advice" (Table 1). The refusers differed significantly from the nonrefusers with regard to the frequency of organic mental syndromes, one of the two most frequent DSM III Axis I diagnoses. Neither adjustment disorders nor "other" diagnoses were significantly different. In the refusers group, diagnosis was DSM III "deferred" in three cases and DSM III "no diagnosis" in 15.

Stated vs. Assessed Reasons. Comparison of the stated versus the assessed reasons for consultation in the "refusers" group reveals three important differences (Table 2). First, only eight patients (8.9%) were recognized as having organic disease by the nonpsychiatric physician, whereas 30 (33.3%) were so assessed by the psychiatrist using DSM III diagnostic criteria. Second, only 16 cases (17.8%) had chronic illness as a stated problem, whereas 43 patients (47.8%) were assessed as having this difficulty. Third, while five patients (5.6%) were judged by the medical consultee to be fearful and anxious, 32 patients (35.6%) were so categorized by the psychiatrist.

TABLE 1

Reasons for Consultation as Assessed by Psychiatric Consultant: Refusers versus Nonrefusers

Assessed variable	Refusers	Nonrefusers	p
Noncompliance	42 (43.30%)	86 (12.03%)	<0.0001
Behavior management	46 (47.42%)	153 (21.04%)	0.0001
Judgment	29 (29.90%)	48 (6.72%)	<0.0001
Chronic illness	47 (48.46%)	248 (34.60%)	<0.02
Suicidal	14 (14.44%)	180 (25.18%)	<0.006
Depression	31 (31.95%)	293 (40.98%)	<0.05
Organicity	33 (34.02%)	144 (20.14%)	<0.007
Severity of psychiatric illness (5 and above)	33 (34.02%)	154 (23.37%)	<0.01
Severity of psychosocial stress (5 and above)	64 (86.48%)	378 (69.61%)	<0.07
Administrative action			
Impaired judgment	13 (13.40%)	9 (1.26%)	<0.001
discharge AMA	10 (10.31%)	11 (1.54%)	<0.001
Axis I diagnosis:			
OMS	38 (39.18%)	191 (26.71%)	<0.010
Adjustment disorder	21 (21.65%)	150 (20.98%)	<0.900
"Other"	38 (39.18%)	374 (52.31%)	<0.015

Discussion

Given the difficulty and frustration that the hospital staff encounters in dealing with the patient who refuses tests and treatment, the strong correlation of refusing with noncompliance, behavior management problems, and questions of impaired judgment is hardly surprising. Refusal may be considered an overt act of noncompliance, one in which the doctor's authority is openly defied. Provoked this way, the physician may counter this challenge to his or her expertise by questioning the patient's judgment or labelling the patient as a behavior management problem, or both. It is at this point that the psychiatric consultant is called in, either in the hope that the psychiatrist will be able to coax the patient into acceptance, or to confirm the suspicion of impaired judgment with documentation of poor mental status.

The reasons cited in the literature for treatment refusal are diverse. They range from overt psychopathological behavior based on delusional premises, to the confusional states of drug intoxication, to impaired memory, cognition, or judgment accompanying an organic brain syndrome (2), to another extreme—an apparently rational and informed decision based on realistic understanding of treatment alternatives. Refusal to undergo treatment may be a legitimate stance

TABLE 2
Reasons for Consultation among Refusers: Stated versus Assessed

Stated reason		Assessed		Statistical significance*
		Yes	No	
Organicity	Yes	8	0	
	No	22	60	.0001
		Yes	No	
Chronic illness	Yes	11	5	
	No	32	42	.0001
		Yes	No	
Anxiety/fear	Yes	5	0	
	No	27	58	.0001

* McNemar's chi-square.

against a high-risk, low-benefit procedure. Between these extremes lies a large gray area in which the religious, sociocultural, and psychological context in which the refusal is made often obscure the distinction between what is rational or irrational; this turns the question of competence to refuse into a value judgment rather than an objective assessment of fact.

While a number of authors have emphasized the role of sociocultural belief systems in motivating treatment refusals (3), others have focused on the failure to establish an effective dialogue with the patient (4, 5). The physician may fail to provide adequate information about the intended regimen or procedure. He or she may misinterpret the patient's silence as a sign of understanding or compound the patient's confusion with a highly technical explanation.

Other factors implicated in treatment refusal include the dissatisfactions and frustrations of prolonged hospital stays and the problems of coping with chronic or terminal illness in which treatments are only palliative at best. Finally, refusal may be construed as a healthy assertion of self, an attempt to regain some measure of autonomy and control in what is an essentially passive and sometimes dehumanizing situation. Refusing may be the only leverage with which a patient can negotiate what happens to him or her during the hospital stay (3).

The role of the psychiatric consultant in such cases is complicated by the legal and ethical dilemmas that the refusal of treatment entails. Nonpsychiatric physicians may legitimately request a psychiatric consultation in order to obtain guidance in treating psychological problems that they do not feel qualified to handle. On the other hand, the consultation process may be abused in that the psychiatrist may be used as a means to persuade the patient to abide by the primary physician's treatment decisions. It has been argued that conflicts between opposing moral values of physician and patient may be effectively masked by the request for consultation (6). Difficult ethical issues are safely evaded by attributing the problem of treatment refusal to psychological instability or lack of judgment. The patient may feel coerced into complying with medical orders in the fear that the psychiatrist may find that he has impaired judgment or is insane (6).

The possible abuses of the psychiatric consultation, however, are offset by its potential benefits. As evidenced here, requests for consultation citing refusal of treatment as a reason uncovered a group of patients with a high percentage of psychiatric morbidity. Refusers as compared to nonrefusers were rated as having greater severity of psychiatric illness and had a greater degree of psychosocial stress. Eighty-two percent of the refusers met criteria for an Axis I diagnosis. The psychiatric consultation process provides access to those patients who would not normally seek psychiatric care. The opportunity to identify, diagnose, and treat these patients that is made possible by the consultation process permits the improvement of medical care the patient receives.

Failure to Suspect Organicity. The single most revealing finding in this regard is the higher frequency of organic mental syndromes among the refusers than among nonrefusers. Although organicity provides a logical and unified explanation of the high correlation of refusing with noncompliance, behavior management, and judgment problems, it is significant that the medical staff was largely unaware of this possibility. Organicity was rarely considered a possible cause of the patient's refusal.

The failure to suspect organicity is of particular concern for patients who refuse to undergo important procedures and tests; the patient's mental as well as physical health is at risk. The diagnosis and possible treatment of reversible causes of organicity is missed and the acceptance of an incompetent refusal of treatment at face value may lead to the withholding of valuable medical care.

In an attempt to conserve the individual's autonomy, the patient's health should not be compromised in the false belief that the individual's right to refuse treatment is being respected (7). While much emphasis has been placed on the guidelines for determining competency for informed consent, the question of competency to refuse treatment has equally important ethical and legal implications (8). "The physician who withholds treatment from an incompetent patient who refuses treatment may be held liable to that patient if the physician does not take reasonable steps to obtain some other legally valid authorization for treatment" (9). However, several authors have argued that legal definitions and guidelines complicate rather than clarify the situation (7, 10–12). As Applebaum and Gutheil point out, "legal conceptions of a right to refuse treatment may not accurately portray the realities of the clinical situation, in which patients' refusal is determined by the dynamics of their illness rather than reflecting a principal exercise of their legal rights" (12).

Refocusing on Unvoiced Concerns. Nonpsychiatric physicians were generally unaware that anxiety and chronic illness may be important determinants of refusal. As the Appelbaum and Roth study noted, the physician would often try to convince the patient to accept without first determining the underlying reasons for the refusal (1). The response of the physician tended not to depend on specific reasons for the patient's refusal, but rather on the medical desirability of the treatment and the possibility of proceeding with treatment despite the patient's objections (1). The failure of the medical staff to appreciate the patient's true concerns underscores the importance of sustaining communication in the face of refusal. Rather than viewing the refusal as an impasse, the physician should consider it a cue to the presence of unvoiced concerns and should refocus attention from the manifest refusal to its possible latent causes (4).

The issues uncovered during the psychiatric consultation process indicate that the ability of the medical staff to understand and effectively manage treatment refusals is hindered by a limited awareness of the psychological determinants of refusal. The implications, however, are even more important for those instances of refusal which, for a variety of reasons, do not result in a request for consultation. For it is in these patients that the undiagnosed and potentially reversible organicity, the unvoiced anxiety, and the problems of coping fail to be addressed. Refusal, whether it be for a major surgical procedure or for a simple blood drawing, should be regarded with a view toward understanding the underlying mechanism.

The multitude of reasons for refusing and the lack of any distinctive demographic pattern limit the categorization of the patient "at risk" for refusal. However, once a refusal does occur, two distinct approaches should be explored: first, the administration of a detailed mental status examination to rule out the presence of organicity when impaired judgment is suspected; second, encouraging the patient in a meaningful and open-ended dialogue where feelings and concerns may be freely expressed.

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VOLUME 52 NUMBER 5 MAY 1985

JUN 18 1985

CONTENTS

GENERAL ARTICLES

Autopsy Findings as a Modifier of Diagnosis-Related Group Classification and Hospital Reimbursement *Jacqueline Heller, M.S., Deborah Friedlander, B.S., and Stephen A. Geller, M.D.* 311

Nomograms for Predicted FEV_1 and FVC in Children, Adolescents, and Adults *Kenneth A. Corre, M.D., James E. Hansen, M.D., and Robert J. Rothstein, M.D.* 315

Red-Cell Size Distribution Analysis: An Evaluation of Microcytic Anemia in Chronically Ill Patients *Frederic J. Kaye, M.D., and Blanche P. Alter, M.D.* 319

An Improved Method to Test the Completeness of Parietal Cell Vagotomy *Gaetano Romeo, M.D., Antonino Giovinetto, M.D., Rosario Calì, M.D., Francesco Basile, M.D., Gaetano Catania, M.D., Francesco Cardì, M.D., and Giorgio Giannone, M.D.* 324

Stress, Pancreatic Perfusion, and Acute Pancreatitis: A Unified Concept of Pathogenesis *Murrel H. Kaplan, M.D., FACG* 326

Enteropancreatic Reflexes 2. The Effect of Jejunal Distension *Alberto Salinas, M.D., Ehud Klein, M.D., Lewis Toth, M.D., and David A. Dreiling, M.D.* 331

continued inside

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THE
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OF MEDICINE

Volume 52
Number 5
May 1985

CONTENTS *continued*

The Effect of Age on Human Exocrine Pancreatic Secretion *David A. Dreiling, M.D., Andrew T. Triebling, M.D., and Moshe Koller, M.D.* 336

The Natural History of Alcoholic Pancreatitis: Update 1985 *David A. Dreiling, M.D., and Moshe Koller, M.D.* 340

Preliminary Observations on Application of Ethibloc in Necrohemorrhagic Acute Pancreatitis in Humans *Francisco D. Torino, M.D., Néstor A. Portillo, M.D., Omar A. Romero, M.D., Martín E. Garaycoechea, M.D., Eduardo Deluca, M.D., and Santiago G. Perera, M.D.* 343

Azathioprine Experience in Severe, Generalized, Recalcitrant Myasthenia Gravis *Peter Kornfeld, M.D., Edward P. Ambinder, M.D., Raymond Matta, M.D., Adam Bender, M.D., A. E. Papatestas, M.D., Harvey Gross, M.D., and Gabriel Genkins, M.D.* 347

Inferior Vena Cava Interruption *Steven M. Keller, M.D., Moshe Papa, M.D., and Joseph R. Wilder, M.D.* 353

CASE REPORTS

Idiopathic Pulmonary Hemosiderosis: The Importance of a Chest Radiograph in Children with Unexplained Anemia *Matthew J. Kuhn, M.D.* 358

Cytomegalovirus Infection and Hemolytic Anemia Due to Glucose-6-Phosphate Dehydrogenase Deficiency *Barry E. Rosenbloom, M.D., Fred P. Rosenfelt, M.D., Hershel Ullman, M.D., and Irwin M. Weinstein, M.D.* 363

Venous Air Embolism: Case Report and Review *Jonathan M. Raskin, M.D., Ernest Benjamin, M.D., and Thomas J. Iberti, M.D.* 367

continued

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CONTENTS *continued*

Abdominal Pregnancy Causing Massive Lower Gastrointestinal Bleeding: Case Report *Alberto Salinas, M.D., Moises Guelrud, M.D., Aholeab Toledano, M.D., and David A. Dreiling, M.D.* 371

Recurrent Nephropathy Associated with Heroin Use *Walter G. Wasser, M.D., Edith Grishman, M.D., Marvin H. Goldstein, M.D., and Michael Gerber, M.D.* 375

Aggressive Juvenile Fibromatosis *Alan M. Schwartz, M.D., John C. Leonidas, M.D., and C. H. Doku* 378

NEUROLOGY NOTES *L. Jay Turkewitz, M.D., editor*

Brain Biopsy: Risks, Benefits, and Indications *Steven Sevush, M.D., and L. Jay Turkewitz, M.D.* 380

PATHOLOGY NOTES *William Thomas, Jr., M.D., editor*

Profile of a Successful Hospital Clinical Parasitology Laboratory *Russell M. McQuay, Ph.D.* 384

RADIOLOGY NOTES *Jack G. Rabinowitz, M.D., editor*

Interventional Radiology of the Biliary Tree: Introduction *John S. Train, M.D.* 387

Percutaneous Transhepatic Removal of a Giant Bile-Duct Stone *Bernard Lewin, M.D., John S. Train, M.D., Sol J. Dan, M.D., and Harold A. Mitty, M.D.* 389

Percutaneous Transhepatic Dilation of a Choledochoenterostomy Stricture *Mika Lidov, M.D., John S. Train, M.D., Sol J. Dan, M.D., and Harold A. Mitty, M.D.* 392

Percutaneous Transhepatic Placement of a Biliary Endoprosthesis *Aryeh L. Stollman, M.D., John S. Train, M.D., Sol J. Dan, M.D., and Harold A. Mitty, M.D.* 395

STUDENTS' CORNER

Crohn's Disease and Pregnancy: A Literature Study *Rosemaria Gennuso, M.D.* 398

THE MOUNT SINAI JOURNAL OF MEDICINE
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Autopsy Findings as a Modifier of Diagnosis-Related Group Classification and Hospital Reimbursement

JACQUELINE HELLER, M.S., DEBORAH FRIEDLANDER, B.S., AND STEPHEN A. GELLER, M.D.

Abstract

In an effort to contain hospital health care cost, the Medicare Act has been modified to include a prospective payment system for hospital reimbursement based on "diagnosis-related group" (DRG) classification. We evaluated the possible effects of the autopsy in determining the correct DRG classification. In a retrospective review of 64 autopsied patients, 20 (31.3%) had different principal diagnoses when we compared medical records abstractions and the autopsy results. Although the DRG classification changed in 12 of these 20 cases (60%), the potential reimbursement, as calculated for both groups, was not significantly changed. Autopsies continue to be valuable in measuring accuracy of clinical diagnoses and can be utilized as a potential quality check of the DRG system.

Since the inception of Medicare in 1965, health care costs in the United States have risen in an almost uncontrolled fashion. The magnitude of inflation in health care costs to Medicare prompted Congress to enact a prospective payment system (PPS) that came into effect nationally on October 1, 1983 (1–4).

The operational cornerstone providing the basis for remuneration under the PPS is the Diagnosis-Related Group (DRG) system, developed by Yale University researchers in the 1970s using funds allocated by the Health Care Financing Administration (HCFA). Under the DRG system, hospitals are reimbursed a predetermined sum for each patient hospitalization based on the patient's diagnosis. The DRG is represented by a number assigned to the patient and includes a variety of diagnoses, which are grouped because they are thought to contribute to similar costs.

All possible diagnoses (about 10,000) listed in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) (5), have been classified into 23 major diagnostic categories based on organ systems. These are broken down into 467 "medically meaningful" groupings. All patients in the same DRG can be expected to evoke a set of clinical responses which will, on a statistical average, result in approximately equal use of hospital resources.

The assignment of a DRG requires items of information about the patient:

1. *Principal diagnoses.* HCFA has adopted the Uniform Hospital Discharge Data Set (UHDDS) which defines principal diagnosis as "the condition established after study to be chiefly responsible for occasioning the admisssion of the patient to the hospital for care" (6)
2. *Complications* or *Comorbidities* (C/C).
3. *Principal Surgical Procedure.*
4. *Age.*
5. *Sex.*
6. *Discharge Status.*

This information should be on the discharge face sheet, which must be filled in by the attending physician or resident. The face sheet is

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From the Class of 1985, Mount Sinai School of Medicine (CUNY) (Heller and Friedlander) and the Lillian and Henry M. Stratton-Hans Popper Department of Pathology of the Mount Sinai School of Medicine (CUNY) (Geller). Address reprint requests to Stephen A. Geller, M.D., Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Los Angeles, CA 90048.

TABLE 1

DRG-Significant Differences in Diagnoses due to Medical Record Error

Case no.	Diagnosis on medical record	Diagnosis on autopsy
1	Paraparesis	Cerebral infarct
2	Congenital factor VIII disorder	Disseminated lymphoma
3	Maintenance of chemotherapy	Widely metastatic adenocarcinoma
4	Cardiopulmonary arrest	Subphrenic abscess
5	Cardiopulmonary arrest	Adenocarcinoma of lung
6	Metabolic acidosis	Hemoperitoneum
7	Atrial fibrillation and flutter	Widely metastatic adenocarcinoma
8	Possible arteriovenous malformation	Aortic insufficiency

TABLE 2

DRG-Significant Differences in Diagnoses due to Diagnostic Errors

Case no.	Clinical diagnosis	Autopsy diagnosis
1	Colonic polyps	Colonic adenocarcinoma arising in colonic polyp
2	Peptic ulcer disease	Ischemic enteritis and colitis
3	Malignant neoplasm of respiratory and digestive system	Metastatic pancreatic adenocarcinoma
4	Small-bowel adenocarcinoma	Gastric adenocarcinoma
5	Craniopharyngioma	Chondrosarcoma of the clivus
6	Metastatic carcinoma, primary, site unknown	Cholangiocarcinoma of liver
7	Malignant neoplasm of extrahepatic bile ducts	Hepatocellular carcinoma with portal vein invasion
8	Malignant neoplasm with unspecified site	Metastatic pulmonary adenocarcinoma
9	Aspiration pneumonia	Metastatic carcinoma in liver
10	Peripheral neuropathy	Metastatic carcinoma in brain
11	Malignant neoplasm of bronchus or lung	Malignant mesothelioma
12	Cerebral calcification	Cerebral infarct

usually reviewed by a medical records abstractor who also reads the entire chart for any errors or omissions. The abstractor then codes all information according to the ICD-9-CM and sends it to a Medicare fiscal intermediary for DRG assignment.

Reimbursement is based on a product of two factors, the DRG weight and the dollar rate. Each DRG weight is an index number representing the relative hospital resources which, on the average, are used for furnishing inpatient services. During an initial three-year transition period, the dollar rate is to be calculated as a function of a federal rate and a hospital-specific rate (i.e., the cost that the hospital incurs). Beginning with the fourth year, 100% of the dollar rate will be based on a national, federally mandated rate. One intent of the transition period is to lighten the financial burden on hospitals with high dollar rates or especially complex case loads (7).

We attempted to determine if the principal autopsy diagnosis, when compared to the discharge face sheet information, would yield significant changes in DRG classification.

The autopsy confirms or refutes clinical diagnoses and provides a means of assessing the appropriateness of medical and surgical therapy, and, in this way, serves to monitor the quality of medical care. The autopsy also is a source for data about recognized diseases, and for the understanding of the natural history of emerging conditions. Information beneficial to the deceased's family becomes available. Other benefits from the autopsy have been reviewed (6–17).

The usefulness of the autopsy has been well documented by studies that confirm discrepancies between anatomical and clinical diagnoses in as many as 8% to 40% of cases autopsied (6, 10, 11). The autopsy is the time-tested vehicle for quality control, education, and research. It is clear that these functions remain necessary and perhaps attain added significance in today's medical world, with its shifting financial climate, rapidly burgeoning information and technology, and changing sociocultural contexts.

Methods

This study was undertaken at The Mount Sinai Hospital, New York, a 1,200-bed urban medical center. The clinical records of all adults who died between January and July 1983 and had autopsies performed were reviewed. Sixty-four clinical records and autopsy reports were reviewed and compared. Approximately 40 cases were unavailable for study. The overall autopsy rate, including adults and children, was less than 20% during 1983. The principal diagnosis for each case was selected on the basis of the definition set forth by the UHDDS. Medical records personnel would employ the same logic if they had the autopsy reports at the outset of the abstracting process. However, since discharge data must be completed

TABLE 3
Comparative DRG Classification and Weights

Case no.	Clinical DRG	Clinical Weight	Autopsy DRG	Autopsy Weight	Effect of autopsy on DRG reimbursement
1	34	.9927	14	1.3527	Increase
2	468	2.1037	468	2.1037	No change
3	468	2.1037	400	2.8272	Increase
4	177	.7422	190	.3379	Decrease
5	203	1.0937	203	1.0937	No change
6	203	1.0937	203	1.0937	No change
7	129	1.5506	207	.8492	Decrease
8	129	1.5506	82	1.1400	Decrease
9	298	.7538	190	.3379	Decrease
10	172	1.2268	172	1.2268	No change
11	138	.9297	82	1.1400	Increase
12	468	2.1037	468	2.1037	No change
13	413	1.0975	203	1.0937	Decrease
14	201	2.7291	201	1.7291	No change
15	406	2.2671	468	2.1037	Decrease
16	81	.8743	203	1.0937	Increase
17	468	2.1037	468	2.1037	No change
18	82	1.1400	82	1.1400	No change
19	17	.8392	14	1.3527	Increase
20	130	.9645	137	.6381	Decrease

Summary: 5 patients: reimbursement increased
8 patients: no effect on reimbursement
7 patients: reimbursement decreased

Weights determined by "Autogrouper" program.

TABLE 4
DRG Reimbursement: Clinical vs. Autopsy Determination

Case no.	Clinical	Autopsy	Difference
1	2716.83	3702.08	−985.25
2	5757.43	5757.43	0
3	5757.43	7737.50	−1980.07
4	2031.26	924.77	1106.49
5	2993.25	2993.25	0
6	2993.25	2993.25	0
7	4243.70	2324.10	1919.6
8	4243.70	3119.96	1123.74
9	2063.01	924.77	1138.25
10	3357.52	3357.52	0
11	2544.41	3119.96	−575.55
12	5757.43	5757.43	0
13	3003.65	2993.25	10.4
14	7469.03	7469.03	0
15	6204.62	5757.43	447.19
16	2392.79	2993.25	−600.46
17	5757.43	5757.43	0
18	3119.96	3119.96	0
19	2296.73	3702.08	−1405.35
20	2639.65	1746.36	893.29
TOTAL	77343.08	76250.81	1092.27
Sample Means	3867.15	3812.54	54.61

Using paired t test:
Null hypothesis H_0: No difference between dollar values medical vs autopsy:
Assume $p = 0.05$ is significant

Results: $t = 0.2570$, $p = 0.5$

DRG reimbursement determined by DRG weight × dollar rate, Federal Regional Adjusted Standardized Amount for the Middle Atlantic Areas (2,736.81).

within 72 hours, autopsy information is generally not available for coding.

We identified 20 cases in which the clinical diagnosis differed from the autopsy diagnosis.

The DRGs for both clinical and anatomic diagnosis were determined in each of the 20 cases, utilizing an approved software package ("Autogrouper"). Data were entered twice for each of the twenty cases; once using the principal diagnosis as established by medical records personnel, and once with the principal diagnosis established from the autopsy report. Thus, two DRGs were generated for each patient, based solely on the use of two different principal diagnoses.

Subsequently, the difference in remuneration was calculated for those cases in which DRGs changed. For purposes of simplicity we utilized the federal rates in our calculations (19).

Results

Principal Diagnosis. Twenty of the 64 charts reviewed (31.3%) demonstrated discrepancies between the principal diagnosis as abstracted from medical records and principal diagnosis as concluded from autopsy reports. In eight cases (12.5%) differences were due to medical record errors in determining the principal diagnosis (Table 1). In 12 cases (18.5%) differences reflected a diagnostic error (Table 2).

DRG Classification. Table 3 shows that the principal diagnosis as determined by autopsy reports affected DRG reimbursement in 12 of the 20 (60%) patients. Reimbursement was increased in 5 cases (25%) and decreased in 7 cases (15%).

DRG Reimbursement. The projected total reimbursement for the 20 patients using the medical diagnosis was $77,343.08, whereas the total reimbursement using the autopsy diagnosis was $76,250.81. The calculated difference is $1,092.27. A paired t test was performed to determine the significance of this difference. A probability value of 0.05 or less was considered significant. Result of the t test reveals that $t = 0.2570$ and that p is greater than 0.5. We therefore did not reject the null hypothesis and concluded that there was no statistically significant difference between the medical and autopsy dollar value.

Discussion

A discrepancy was found in 20 of 64 cases (31.3%) when we compared the principal diagnosis in the clinical chart with that established by autopsy. Although the 64-chart sample was small, the error rate was great. Indeed, in 12 of the 64 cases (19%), a clinically significant and DRG-significant error was documented. In 8 cases (12.5%), the discrepancies were due to medical record errors. In five of these cases (patients 3, 7, 8, 9, and 11), the physician failed to follow the definition of principal diagnosis as set forth by the UHDDS. For example, in two cases (patients 7 and 8), the physicians noted the mechanisms of death, i.e., cardiopulmonary arrest, rather than stating the reason for hospital admission. In the other three cases (patients 3, 9, 11), physicians noted complications or comorbidities as the principal diagnosis, and these errors were not noted by the abstractors. The principal diagnoses were legitimate in 3 cases in this group, since they conformed to the UHDDS definition; however, the choice of wording was poor and reflected an incomplete review of the chart.

The prospective payment system is a radical change in reimbursement policy which will greatly affect every hospital's finances. Our study suggests that the process of determining the principal diagnosis is too subjective. A more objective audit and review of procedure is needed. If the DRG classification is going to accurately reflect the allocation of hospital resources, there must be more precise criteria for evaluation of methods and personnel.

The utilization of autopsy data for quality control of the DRG system does not completely satisfy the need, since less than 15% of deaths are autopsied (18). However, if autopsy data were required for determining DRGs, statistics would be generated that could be useful for monitoring the system and possibly for cost containment. While the limitations of our study are evident (biased design and small sample), the 31.3% disparity between medical records and autopsy diagnoses leaves no doubt that further study is warranted.

Physician error in documenting diagnoses is well recognized, and we have previously documented the effect on DRG determinations (19). Many physicians are not aware of the guidelines for classifying DRGs, and their performance in this regard is usually not studied by peer-review committees. In addition, there is little incentive for physicians to improve, since the final and determining evaluation is by medical records personnel. Clearly, utilization of autopsy findings would be the most objective method for checking physician performance. The documentation process, as it is now practiced, is highly subjective and lacks incentives for improving accuracy.

In our study, there was relatively little impact of the autopsy-derived DRG on potential remuneration. Does this mean that the autopsy has no role? Clearly, the autopsy remains the single most reliable means of confirming the accuracy of clinical diagnoses, and increasing utilization of this quality-assurance tool is clearly justifiable. Further, as we have indicated, this can only be regarded as a pilot study and greater numbers of cases may show a significant monetary impact.

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Nomograms for Predicted FEV_1 and FVC in Children, Adolescents, and Adults

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Abstract

The application of reference normal lung function values is widespread. The numerous regression equations and the few nomograms for predicted FEV_1 and FVC in use conflict. Many do not meet the requirements of the American Thoracic Society and are often useful only for limited age groups. After reviewing the inadequacies of the various regression equations, it is concluded that the recent regression equations of Knudson et al are most applicable for clinical use. New nomograms for FEV_1 and FVC are presented for white male and female spirometric mean values, with standard errors for children, adolescents, and adults. Simple alterations are recommended for application of these nomograms to various ethnic groups.

Predicted normal values for spirometric tests are essential for clinical interpretations, as deviations from normal values have well-known diagnostic and therapeutic implications. In the last three decades, many investigators have published regression equations for Forced Expiratory Volume in One Second (FEV_1) and Forced Vital Capacity (FVC) which give conflicting normal values. Optimally, each laboratory should select and measure normals from its own population for reference values, but this is usually impractical. Thus, a widely applicable set of normal values is needed.

The range of values for most pulmonary function tests in a population of normal subjects is broad (1). Values for FEV_1 and FVC vary with age, sex, height, altitude, cigarette smoking, gravid state, race, and disease, although most studies have eliminated pregnancy and disease from their data base and have reported results primarily in white populations (1, 2). The addition of weight contributes little to predictive accuracy (3). Because lung volumes and flow rates vary predominantly with age, height, and sex (1), these factors are utilized in nearly all regression equations (4). The resulting reduction in the range of predictive values allows for the selection of more meaningful lower limits of normal. Nevertheless, the regression equations and predicted normal pulmonary function values differ substantially from study to study (4, 5). Differences in equipment, measurement technique of FEV_1, ethnic mix, and inclusion of past or present smokers in the data base account for the major discrepancies. After other groups set the ground work (6, 7), the American Thoracic Society (ATS) established criteria for performing spirometry and measuring the FEV_1 (8). Some have suggested that less stringent criteria may be acceptable outside the pulmonary function laboratory (9). Subsequently, Gardner et al (10) tested commercially available spirometers and identified those that meet ATS qualifications. However, what remains unresolved is the issue of which series best represents the average healthy population.

Selecting Reference Normal Values. In selecting the optimal prediction equations, each clinician must weigh both the adequacy of methodology and the applicability of the reference pop-

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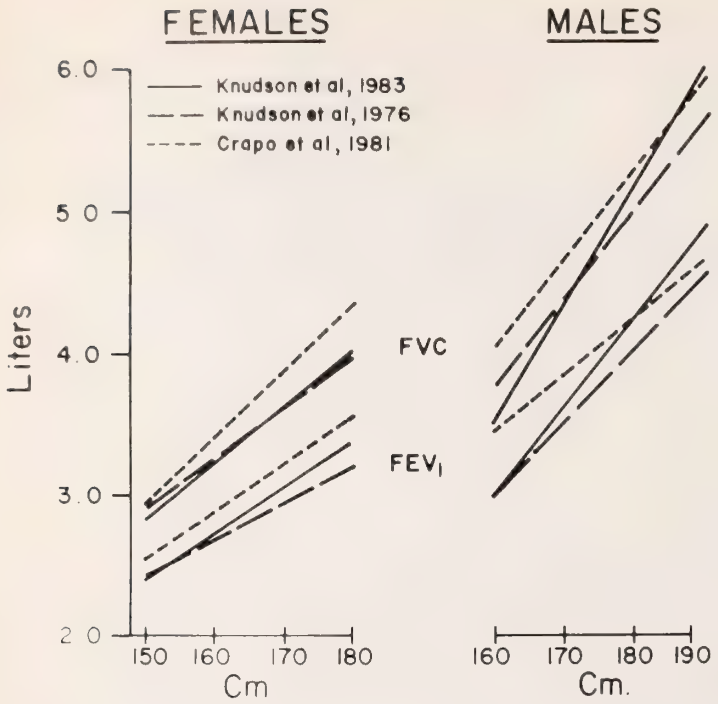

Fig. 1. Comparisons of FVC and FEV$_1$ in males and females 40 years of age of varying heights. From Knudson et al 1976 (11), revised Knudson et al 1983 (14), and Crapo et al 1981 (4).

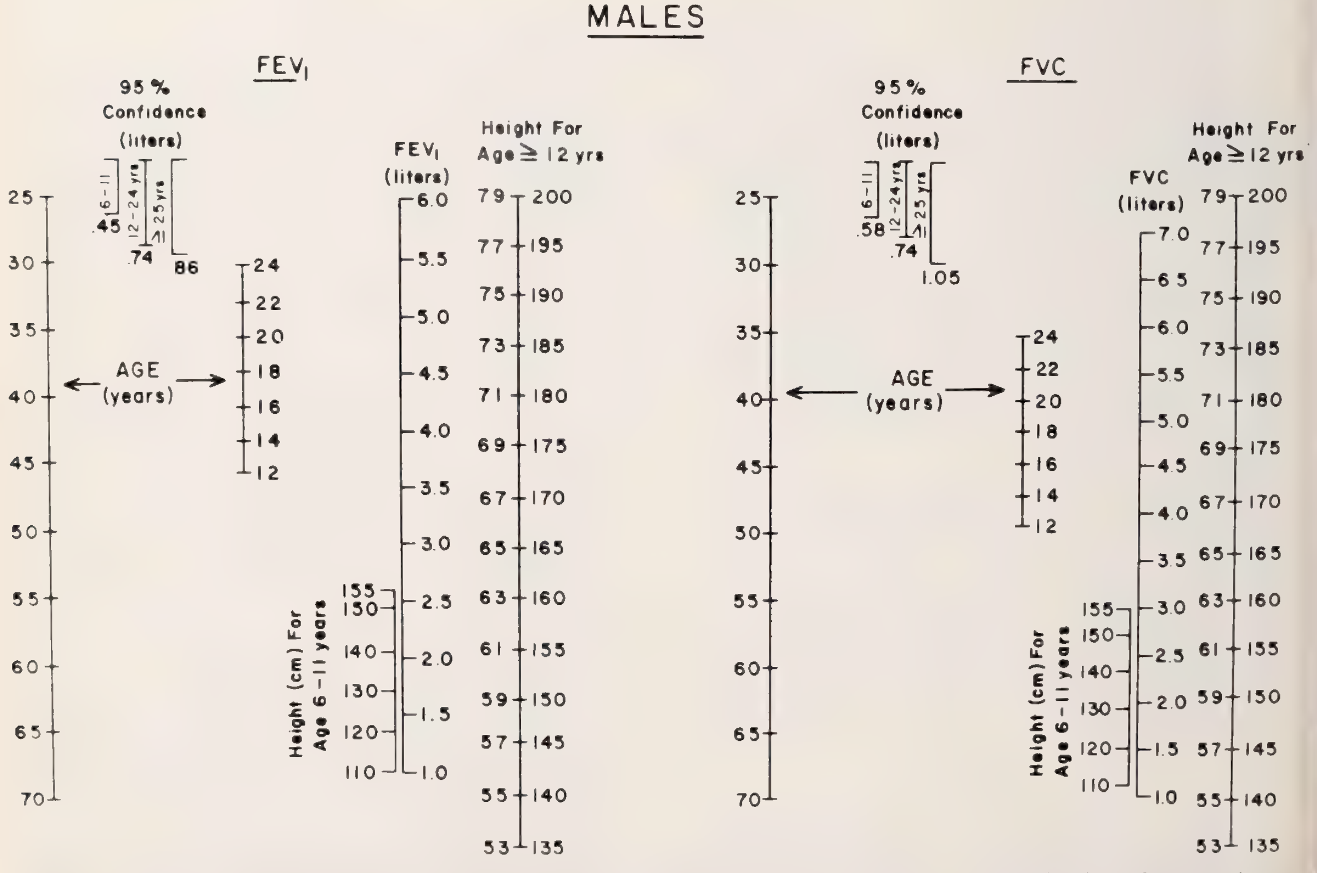
MALES
FEV$_1$
95 %
Confidence
(liters)
6-11
12-24 yrs
≥ 25 yrs
.45
.74
.86
25
30
35
40
45
50
55
60
65
70
AGE
(years)
24
22
20
18
16
14
12
FEV$_1$
(liters)
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Height (cm) For
Age 6-11 years
155
150
140
130
120
110
Height For
Age ≥ 12 yrs
79 200
77 195
75 190
73 185
71 180
69 175
67 170
65 165
63 160
61 155
59 150
57 145
55 140
53 135
FVC
95 %
Confidence
(liters)
6-11
12-24 yrs
≥ 25 yrs
.58
.74
1.05
25
30
35
40
45
50
55
60
65
70
AGE
(years)
24
22
20
18
16
14
12
FVC
(liters)
7.0
6 5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Height (cm) For
Age 6-11 years
155
150
140
130
120
110
Height For
Age ≥ 12 yrs
79 200
77 195
75 190
73 185
71 180
69 175
67 170
65 165
63 160
61 155
59 150
57 145
55 140
53 135

Fig. 2. There are 2 age ordinates for each nomogram. For older children and men, align a straight edge from the person's age to their shoeless standing height. The edge crosses the FEV$_1$ or FVC ordinate at the mean value for white person of that age and height. For younger children, the FEV$_1$ and FVC are directly horizontal to the height ordinate, as age does not affect variability in this group. By subtracting the age-specific 95% confidence interval from the mean value, the lower limit of normal for the white male is obtained. An additional 15% is subtracted to attain the lower limits of normal for nonwhite persons.

ulation to his or her own population. Most studies (4) can be eliminated from serious consideration because they include past or present smokers and nonsmokers, utilize inappropriate equipment or techniques for measurement of the FEV$_1$, or include subjects of several races without discriminating. Some studies include only one sex, fail to report maximal FEV$_1$ and FVC, make measurements at high altitude, or lack adequate explanation of methodology. The majority of studies do not include all age groups in their data base. We feel the choice narrows to the series of two groups of investigators: The groups reported by Crapo et al (4) and Knudson et al (11) are best, but which group is optimal is still subject to controversy (12, 13).

In order to more closely meet ATS requirements, Knudson et al (14) reviewed their 1976 data and recalculated FEV$_1$ and FVC, establishing more accurate equations for white children, adolescents, and adults. This change, however, does not rectify absolute differences from Crapo et al (4) (Fig. 1). Because Crapo's data involve measurements at several thousand feet above sea level on Mormon adults only, and may be less ethnically diverse, we selected the latest equations of Knudson et al (14) for reference normal values.

Nomograms. We present the data of Knudson et al (14) in nomogram form (Figs. 2, 3), because nomograms are simple and quick to use in the emergency department, office, or pulmonary function laboratory.

There are two age ordinates for each nomogram. For older children and adults, align a straight edge from the patient's age to his or her measured shoeless height. The edge crosses the FEV$_1$ or FVC ordinate at the mean value for a person of that age and height. For younger children the FEV$_1$ and FVC are directly horizontal

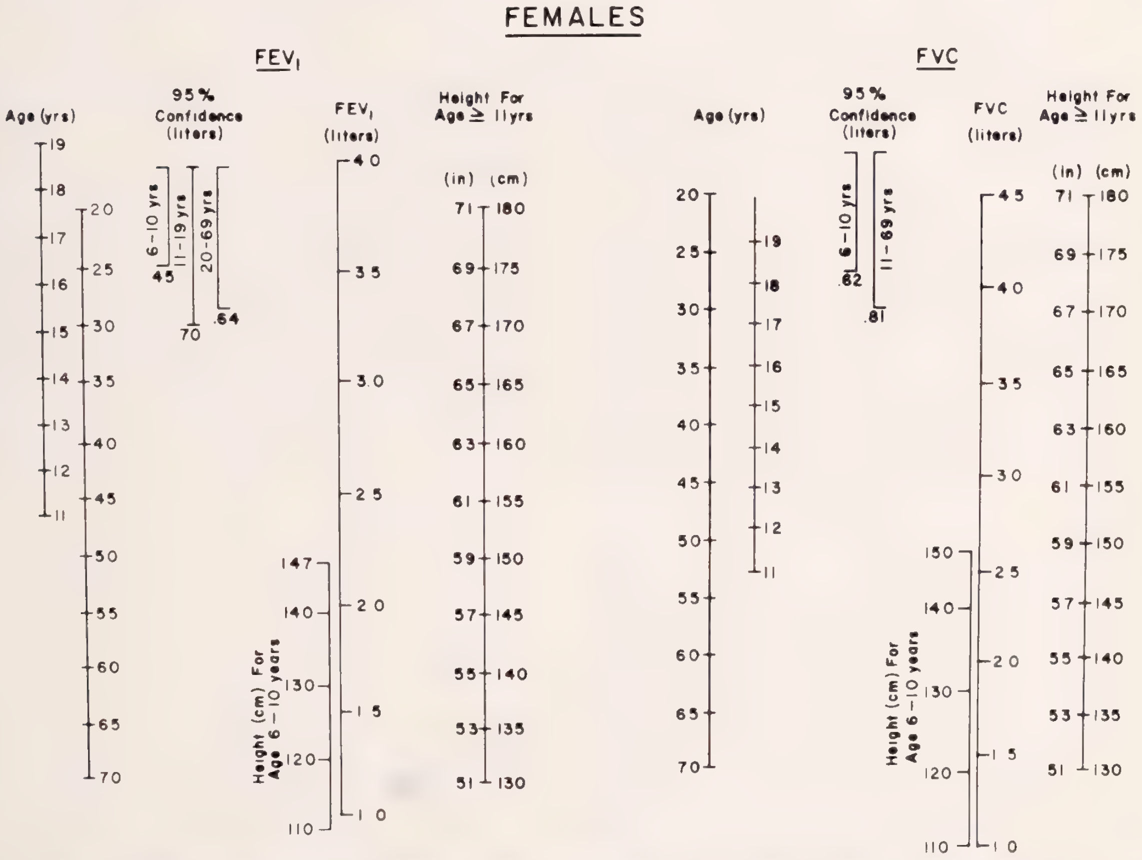

Fig. 3. There are 2 age ordinates for each nomogram. For older children and women, align a straight edge from the person's age to their shoeless standing height. The edge crosses the FEV$_1$ or FVC ordinate at the mean value for a white person of that age and height. For younger children, the FEV$_1$ and FVC are directly horizontal to the height ordinate, as age does not affect variability in this group. By subtracting the age-specific 95% confidence interval from the mean value, the lower limit of normal for the white female is obtained. An additional 15% is subtracted to attain the lower limits of normal for the nonwhite persons.

to the height ordinate, as age does not affect variability in this group (14). Assuming a normal population distribution, 95% of all normal persons (95% confidence limit) will have a FVC and FEV_1 that falls above the mean graph value minus 1.65 times the standard error (11). The value of the standard error times 1.65 (labeled 95% confidence) for each age group appears on the nomograms. For example, normal white women 40 years of age with a height of 65 inches have a mean expected FEV_1 of 2.90 L (Fig. 3). This value (2.9 L) minus the 95% confidence limit (0.64 L) equals the lower limit of normal for a woman of this age and height (2.26 L).

Spirometric studies using the same equipment have consistently shown FEV_1 and FVC which are 10% to 15% less in adult black men and women than their white counterparts of the same age, sex, and height (3, 15–18). Similar reductions have also been measured in Asians (18, 19) and nonwhite children (3). Therefore we suggest that 15% be subtracted from the lower limits of normal for FVC and FEV_1 values for all blacks and Asians.

Acknowledgments

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Red-Cell Size Distribution Analysis: An Evaluation of Microcytic Anemia in Chronically Ill Patients

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Abstract

Red-cell size distributions were obtained electronically to differentiate iron deficiency from anemia of chronic disease and β-thalassemia trait in patients with microcytic anemias. We examined 17 patients with iron deficiency, 17 with anemia of chronic disease (12 with microcytic indices), 17 normal controls, and 8 individuals with β-thalassemia trait. Red-cell volume histograms were obtained with a Coulter C-1000 Channelyzer, and the mean cell volume (MCV) and coefficient of variation (CV) of the cell volumes were calculated. The subset of patients with the anemia of chronic disease and microcytic indices may constitute a diagnostic problem requiring a hematologic consultation and an invasive procedure, bone marrow aspiration for determination of iron stores. In this study, 16 of the iron deficiency patients were correctly identified because of abnormally large CVs. Patients with anemia of chronic disease had CVs close to the normal range, as did those with β-thalassemia trait. Size distribution calculations are now available automatically on commercial instruments, and thus provide a simple test which distinguishes iron deficiency from anemia of chronic disease and β-thalassemia trait.

Evaluation of microcytic anemias may sometimes be a problem in the chronically ill patient. We have studied the use of red-blood-cell size distribution analysis as a simple technique to help differentiate among three common causes of microcytic anemia: iron deficiency, anemia of chronic disease, and β-thalassemia trait. Examination of the peripheral blood smear and red-cell indices alone cannot establish the diagnosis of iron deficiency, because the anemia of chronic disease is also occasionally associated with a hypochromic, microcytic picture (1). In addition, interpretation of serum iron and total iron-binding capacity and ferritin levels, although useful in the young, healthy population, becomes less reliable in the elderly and in patients who have multiple, complicated medical problems (2, 3). For these reasons, bone marrow aspiration for histochemical staining of iron has remained the reference point for the diagnosis or exclusion of iron deficiency. Unfortunately, this is a cumbersome test for the physician and it is uncomfortable for the typical patient.

Among the microcytic anemias, iron deficiency is characterized by a particularly striking variation in red-cell size (anisocytosis) as observed on examination of the peripheral blood smear. Particle sizing technology provides a quantitative measure of anisocytosis, and has been shown to successfully differentiate the microcytosis of patients with β-thalassemia trait from those with iron deficiency (4–8). More recently a comparison of the red-cell volume distribution in patients with microcytic iron deficiency and normocytic anemia of chronic disease (mean MCV, 86 ± 6 fl) showed increased heterogeneity in the iron deficiency group (9). In addition, use of this technique has been recommended to monitor the effective

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treatment of both iron deficiency and macrocytic anemias (4, 10).

In this paper we describe studies of red-cell size distribution in the particular subgroup of patients with anemia of chronic disease having microcytic red-cell indices (mean MCV, 74 ± 4 fl), and compare their red-cell volume distribution patterns to those of patients with β-thalassemia trait, iron deficiency, and normal controls. This test may be useful in reducing the need for bone marrow examination to determine iron stores in selected chronically ill patients.

Patients and Methods

Thirty-four adult patients of the medical service of The Mount Sinai Hospital, of both sexes and various ages, were studied. Of these, 17 patients had iron deficiency, documented either by bone marrow aspiration showing absent iron stores (9 patients) or by the finding of low serum iron, a transferrin saturation ratio <11%, and an appropriate clinical response to iron therapy. The mean hemoglobin level in these patients prior to treatment was 8.7 gm/dl.

The other 17 patients had anemia of chronic disease (12 had MCV <80 fl; 5 had MCV ⩾80 fl) by the following criteria: all had an identified chronic disease, including active typical and atypical mycobacterial infections, bacterial endocarditis, Crohn's disease, chronic urinary tract infection, and collagen vascular disease. Of the 17 with chronic disease, 10 had bone marrow aspiration that showed increased iron stores. The remainder had depressed levels of both serum iron and total iron binding capacity, but with transferrin saturation ⩾17% (mean, 24%) without response to iron therapy. The mean hemoglobin level of this group was 9.4 gm/dl. No patient had a family history of anemia or thalassemia trait. Hemoglobin electrophoresis and quantitation of A_2 and F was available in 10/12 of the anemia of chronic disease subjects with MCV <80 fl and gave normal results.

Eight samples from patients with known β-thalassemia trait were obtained from Dr. Patricia Giardina of the New York Hospital Pediatric Hematology Center. These individuals were asymptomatic with a mean hemoglobin level of 11.6 gm/dl.

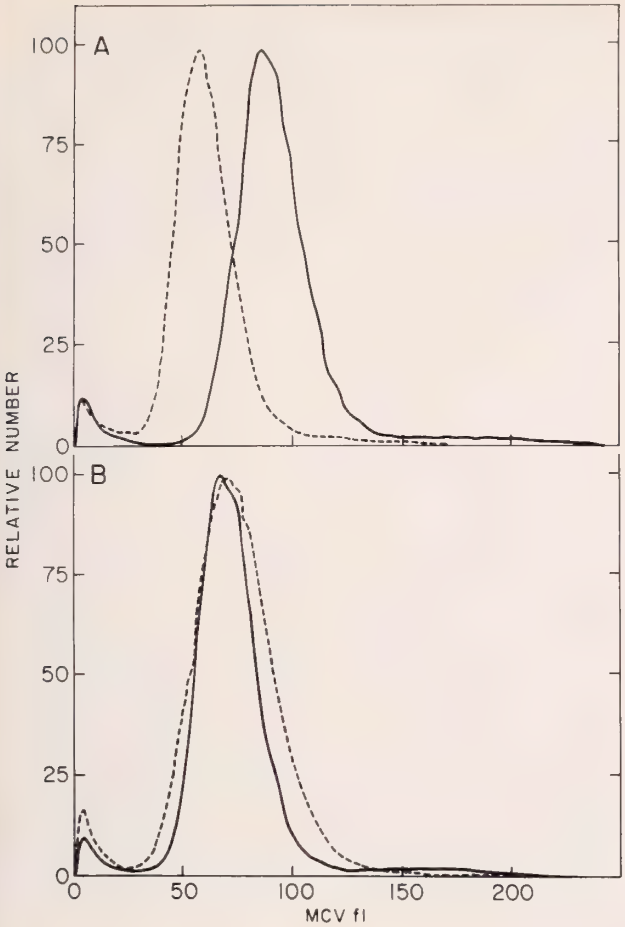
The control patients were selected at random from age- and sex-matched hospitalized patients without apparent hematologic disease, and from house officers. The mean hemoglobin level of this group was 13.7 gm/dl. The median age of the control group was 58; of the iron deficient group, 54; of the chronic disease group, 62; 7 or 8 patients in each group were over the age of 65.

Venous blood was obtained from specimens sent in EDTA anticoagulated tubes to the hematology laboratory for complete blood count (CBC) determination. Procedures were approved by the Research Review Committee of the Mount Sinai School of Medicine. No patient had received a blood transfusion in the 4 months prior to the time the specimens were obtained. Blood (10 μl) was diluted by a factor of 10^5 in Isoton solution and analyzed with a Coulter C-1000 Channelyzer attached to a Model ZBI counter (Coulter Electronics, Hialeah, FL). Calibration was performed with whole blood as outlined in the manual instructions. The aperture was 70μ, base channel threshold was 5, aperture current was 1 ma, and amplification was 1. The edit function was on. A red-cell volume histogram was obtained on each patient and calculations of the red-cell volume mean (m), median, mode, standard deviation (SD), and coefficient of variation (%CV = 100 × SD/m) were performed as described by others (4, 6). Statistical analyses were performed with PROPHET, a time-sharing computer sponsored by the Division of Research Resources of the National Institutes of Health.

A parameter similar to the coefficient of variation (%CV) which we used is now available on some instruments used in clinical laboratories. It is called RDW, or red-cell distribution width. The actual mathematical algorithm used by each company differs and is not available publicly. Our data are presented as %CV, but RDW would provide similar (albeit not identical) information. The important features are differences from normal values.

Results

Red-cell volume histograms for iron deficiency, anemia of chronic disease, β-thalassemia trait, and a normal control were compared (Fig. 1). The wider curve in iron deficiency, as compared to the other groups, graphically demonstrates the increased anisocytosis seen in this disease and is reflected in the increased calculated %CV. The small peak on the left of each histogram represents platelets. In normal persons and the anemia of chronic disease the pattern tends to return to baseline between the platelets and the red cells. The elevated baseline on the left of the β-thalassemia trait and iron deficiency tracings is probably due to red-cell fragments, which are seen on the blood films from these patients. Fragments in hemolytic anemia appear in this region of the his-



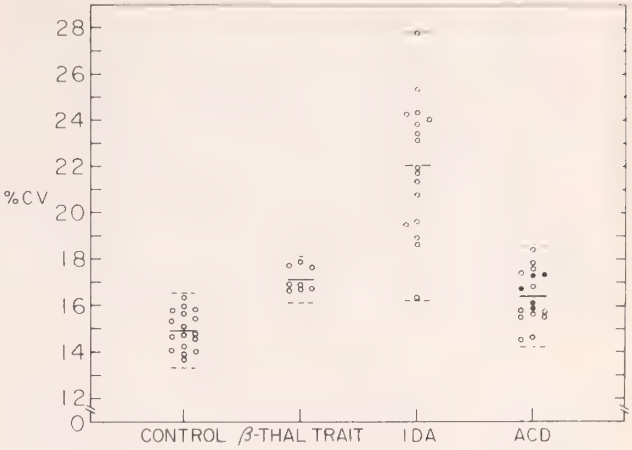


Fig. 1. Left A Red-cell size histograms of blood from β-thalassemia trait (----) and normal (———). **B** Red-cell size histograms of blood from iron deficiency (----) and anemia of chronic disease (———).

Fig. 2. Right Coefficient of variation (%CV) of red-cell volume distribution in control, anemia of chronic disease (ACD), iron deficiency anemia (IDA), and β-thalassemia trait groups; mean (———) and two standard deviations (----). For ACD: patients with MCV <80 fl (○); patients with MCV ≥80 fl (●).

togram (11), and thus we infer that the fragments in iron deficiency are also seen on the histogram. The patterns shown here for each patient were highly reproducible, in agreement with previous studies by Bessman (12).

Calculation of %CV was much more reliable than visual inspection of the curves for accurate characterization of each patient, since the %CV depends on the MCV value. The cause of the slight right skew of the distribution curves seen in most histograms may be due to a combination of events, including the contribution of a small cohort of reticulocytes, the existence of low titer agglutinins in many subjects that may cause a few doublets to pass through the aperture together, nonaxial particle flow through the aperture, and, possibly, actual production of cells in a nongaussian distribution (13). For our calculation of %CV we assumed that the curve followed more closely a log-normal distribution as described by England and Down (10). Calculations based on a gaussian distribution, however, gave comparable results.

In our 34 patients, the mean CV in the control group was 14.9 ± 0.8%, actual range of 13.7 to 16.3 and calculated 2SD range of 13.3% to 16.5% (Table 1, Fig. 2). In the chronic disease group, the mean CV was 16.4 ± 1.1%, significantly higher than in the control group. However, considerable overlap was present, and thus anemia of chronic disease was indistinguishable from normal in any one person. In the 8 patients with β-thalassemia trait, the mean CV was 17.1 ± 0.5%, and all values were above 16.5%. Thus, the β-thalassemia trait patients were minimally distinguishable from normal.

The important distinction was between iron deficiency and anemia of chronic disease. The mean CV in the iron deficiency patients was 22.0 ± 2.9%, range 16.3% to 27.7%. The range in the chronic disease group was 14.5% to 18.4%. Only one value in the iron deficiency group was below

TABLE 1

Red-Cell Size Analyses

Diagnosis	N	MCV fl*	%CV*	%CV range	*p*†
Control	17	89 ± 4	14.9 ± 0.8	13.7–16.3	
ACD					
all	17	76 ± 6	16.4 ± 1.1	14.5–18.4	0.0005
microcytic	12	74 ± 4	16.3 ± 1.3	14.5–18.4	0.002
IDA	17	69 ± 8	22.0 ± 2.9	16.3–27.7	0.0001
β-thal trait	8	63 ± 2	17.1 ± 0.5	16.7–17.8	0.0001

ACD, anemia of chronic disease; IDA, iron-deficiency anemia; β-thal trait, β-thalassemia trait.

* Mean ± 1 SD.

† Student *t* test; %CV in each group compared to control.

18.4, and this was 16.3%. The next lowest values in this group were 18.6% and 18.9%, and all others were above 19%, a value never found in any group except iron deficiency. The subgroup of 12 anemia of chronic disease patients with MCV below 80 fl had the same range as the entire group. We were thus able to identify correctly 16 of the 17 patients with iron deficiency, and distinguish them from the anemia of chronic disease, β-thalassemia trait, and normal controls.

Discussion

Exclusion of the diagnosis of iron deficiency anemia continues to be a difficult problem in the elderly out-patient population. Often these patients are being followed for other medical problems that may be associated with the anemia of chronic disease. Current tests for iron deficiency, including iron, total iron binding capacity, and serum ferritin, are less reliable in this group of patients, and thus bone marrow aspiration is often required. An additional test is needed that is simple and specific for the distinction of iron deficiency from the anemia of chronic disease.

Bessman and Feinstein have previously demonstrated the usefulness of sizing analysis to discriminate among patients with iron deficiency and thalassemia trait (6). In addition, Bessman has also studied patients with the anemia of chronic disease. However, the red cells of those subjects were normocytic, with a MCV range of 82–94 fl (12) in one study and a mean MCV of 86 ± 6 fl (9) in another study. In our series 12 patients had microcytic, hypochromic anemia and low serum iron attributable to the anemia of chronic disease. It is this population that constitutes the major difficulty in excluding the diagnosis of iron deficiency by current noninvasive testing. Using red-cell size distribution analysis (CV) we were able to distinguish 16 of 17 patients with iron deficiency from the anemia of chronic disease, in spite of the presence of microcytosis in these latter patients. In addition, we confirm the usefulness of this method to discriminate subjects with iron deficiency anemia from those with β-thalassemia trait and from well subjects.

The increased degree of anisocytosis seen in patients with iron deficiency has been attributed to the progressive state of net iron loss and successively smaller cohorts of red cells (2). Inherent in this process is the possibility that a steady state may occur, dietary intake equalling iron loss. If this situation were to continue over a 3–4 month period the CV, that is, the red-cell volume heterogeneity, would presumably decrease toward normal. In our study of 17 iron deficient patients, 16 had increased %CV. Thus, a normal %CV in the presence of bona fide iron deficiency is a rare event. An additional useful application of this technique is the study of a patient who has been started on iron therapy just prior to obtaining blood samples for serum iron or ferritin. Cell sizing will still identify such patients with iron deficiency and help guide further therapy. In fact, the %CV will rise while the red-cell population contains a mixture of normal and iron-deficient cells.

There are several important limitations to its application, however, most notably the exclusion of any patient who has received a recent blood transfusion. In addition, the presence of underlying liver disease, alcoholism, combined nutritional deficiency, or other disorders known to result in RBC anisocytosis will restrict application of this analysis. Red-cell volume CV is nevertheless a rapid, simple test which helps separate iron deficiency from anemia of chronic disease. More recent blood count instruments include red-cell size distribution analyses on their printout as a red-cell distribution width (RDW). These automated instruments thus add a new dimension to the examination of erythrocytes. The data described by us indicate the usefulness of this new form of analysis.

Acknowledgments

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An Improved Method to Test the Completeness of Parietal Cell Vagotomy

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Abstract

An improvement of the Grassi technique to test the completeness of parietal cell vagotomy by intraoperative transoral measurement of gastric mucosal pH is presented. This new method does not require gastrotomy. Preliminary results in 30 patients show no increased morbidity and no incidence of ulcer recurrence at maximum follow-up of 24 months.

Parietal cell vagotomy is currently accepted by most surgeons as the procedure of choice for the elective treatment of duodenal ulcer (1–3). Although mortality and morbidity have been shown to be very low, recurrence rate remains higher than after other procedures at 5 or more years after surgery. It is generally believed that incomplete vagotomy is the major factor responsible for ulcer recurrence after vagotomy (2). This hypothesis is supported by the fact that results improve along with the surgeon's experience and that patients with recurrent ulcer respond to subsequent revagotomy.

Intraoperative tests for the evaluation of the completeness of vagotomy have long been used (4). Nowadays, colorimetric tests (5) are rarely used because of their limited practical value; electromanometric and pH metric tests are still selectively used. The electromanometric test (6), which measures intragastric pressure after electrical stimulation of the denervated area of the stomach, gives neither precise distal delimitation of the acid-secreting mucosa nor the exact location of the intact vagal branches. The pH metric test described by Grassi (7) uses a pH probe inserted through a gastrotomy to locate the areas of gastric mucosa with high pH. Its disadvantage is that it requires a gastrotomy, with attendant potential complications. We have tried to improve the Grassi test, eliminating the need for the gastrotomy. The test was also aimed at verifying the accuracy of our technique of parietal cell vagotomy.

Material and Methods. The patients selected for this study were 22 males and 8 females with a history of ulcer disease who failed to respond to medical treatment. All patients had preoperative upper gastrointestinal endoscopy documenting active duodenal ulcer. Of the 30, 6 patients had one previous episode of bleeding which required hospitalization. Three patients were found to have hemoglobin below 10 gm per 100 ml at the time of preoperative workup. No patients had pyloric stenosis or perforation. The mean age of the patients was 42.

Anticholinergics and H_2 blockers were avoided before and during surgery to avoid interference with the intraoperative test. Once the patient was positioned on the operating table, a pH electrode Beckman no. 39043 was inserted through the nose into the stomach. A Beckman reference electrode was put into the skin of one of the patient's arms and wet with a constant saline infusion. The 2 electrodes were connected to a Century SS 1 Beckman pH meter. A nasogastric tube was positioned into the patient's stomach and connected to a 3-way stop-cork. Sterile water was used to wash out the gastric cavity. The surgeon could

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easily check the position of the exploratory electrode once the abdomen had been entered.

Preliminary readings of the pH obtained from the stomach contents at the beginning of the procedure showed an average pH of 2. No patient had a pH higher than 3.5. A subcutaneous injection of pentagastrin (6mcg/kg) was administered about 30 minutes before the completion of the parietal cell vagotomy. When the procedure had been partially completed, the gastric cavity was repeatedly washed out with sterile water. The pH was then tested in the various areas of the gastric mucosa systematically by probing the stomach wall. All the surface areas of the fundus and body of the stomach were examined with special attention to the area of the fundus and the antrofundic mucosal boundary.

Vagotomy was considered complete when no areas of mucosa were found with pH below 5. It was assumed that mucosal pH below 5 was indicative of intact vagal fibers that needed to be searched for and resected. Proximal denervation was extended all around the distal esophagus for about 5 cm from the esophageal gastric junction. The lower limit of denervation was selected at the area where the main branch of the anterior and posterior nerves of Latarjet intersected the gastric curvature. All branches going proximal to the gastric body were divided. No gastric drainage procedures were performed.

Results. After completion of the parietal cell vagotomy, 27 (of 30) patients showed mucosal pH about 5 in the denervated gastric areas. Small areas of residual innervation with pH markedly below 5 were seen in 3 patients, at the end of the procedure. In one of these cases, the residual innervated area was located in the fundus behind the esophageal gastric junction. It was supplied via a thin branch of the posterior vagus located behind the distal esophagus. The pH of this area rose to about 6 once this branch was sectioned. In the other 2 cases, the residual innervated area was seen on the greater curvature in the passage between the antrum and gastric corpus. In both cases, further section of anterior (1 case) and posterior branch (1 case of Latarjet's nerves) corrected this problem.

Follow-up of this group of patients for a period of 3–24 months has shown no recurrence of ulcer symptoms. Two patients were re-endoscoped because of early postprandial discomfort and were found to be free of ulcer.

Discussion. We, with others (8, 9), believe that intraoperative testing for completeness of vagotomy is a valuable technique if it can be performed easily and reliably. Several benefits can be expected from the routine use of the test:

- It offers an intraoperative guideline to assess the completeness of parietal cell vagotomy.
- It improves the surgical technique of vagotomy, especially at resident's level.
- It gives an objective physiological measurement of possibly prognostic significance.
- It reduces ulcer recurrence.

Our method represents an improvement over the Grassi test, since it is simple to perform and does not require gastrotomy. In 3 of 30 patients our technique enabled us to avoid what would probably have been an incomplete vagotomy. It is impossible to speculate whether this residual area could have caused an ulcer recurrence. The test did not significantly prolong the operation and no complications were associated with its use. To confirm whether the incidence of recurrent ulcer can be minimized by the use of this technique will require large numbers of patients and longer follow-up. We consider the preliminary result very encouraging and strongly advocate the use of this intraoperative test.

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Stress, Pancreatic Perfusion, and Acute Pancreatitis: A Unified Concept of Pathogenesis

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Abstract

The pathologic alterations observed in the acute inflammation of the pancreas, regardless of etiology—gallbladder disease, alcoholism, thermal changes, infections, trauma, postoperative, emotional, scorpion bites—suggest cellular infarction. Clinical and experimental evidence proposes that the common denominator is a low-flow state produced by the nonspecific effects of the various stressors. Stated in terms of hemodynamic possibilities, this low-flow state can be translated into splanchnic vasospasm, hypovolemia, and other hypoxic abnormalities.

The appreciation of the basic pathogenetic mechanism is important in the recognition of the disease as well as the institution of early therapy. The hypothesis of ischemic stress dictates therapeutic measures which are directed toward maintaining and improving visceral blood flow and pharmacologic stabilization of membranes by steroids as well as toward development of agents blocking the many noxious polypeptides, such as the depressant myocardial factor, bradykinins, and antisurfactants, which appear to be poured into the circulation by the ischemic and necrotic pancreatic tissue.

One of the most recent statements summing up our knowledge of the cause of pancreatitis is this: "From a clinical standpoint, although we are aware of the association of certain conditions associated with pancreatitis, such as gallstones, and alcoholism, we are in the dark as to the pathogenesis of pancreatitis associated with either of these etiological agents" (1).

Since 1901, gallbladder disease has been accounted one of the primary etiologic factors in acute pancreatitis. In the annals of gastroenterology, the name of Opie (2) is remembered for so impressing his colleagues with this causal connection that the idea has endured for decades.

However, Longmire in 1958 (3) reported two cases of acute pancreatitis in heterotopic pancreatic tissue in which no evidence of obstruction or reflux could account for the pathology. This observation confirmed my suspicions that gallbladder disease and acute pancreatitis could be associated, but not by a cause-and-effect relationship (4). Moreover, it is common knowledge that acute acalculus or acute calculus cholecystitis can occur in patients without pancreatitis, just as one sees pancreatitis in the absence of gallbladder disease. Thus, there is also no necessary interdependence between acute cholecystitis and pancreatitis.

In applying these observations to the etiology of acute pancreatitis, it is of paramount importance to refer to the pathology of the disease to note any characteristic or finding which would pinpoint specific etiology. In my interrogation of many pathologists by questionnaire (5), I learned that no distinguishing feature could be pinpointed by gross or microscopic examination to differentiate one cause from another. The absence of distinctive pathologic findings led to the unified concept of pathogenesis I have proposed.

Furthermore, in reviewing the literature of the etiology of diseases of the other organs of the upper gastrointestinal tract, it is noteworthy that

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many of the causes precipitating acute pancreatitis are responsible for acute inflammation of the stomach (6), duodenum, liver (7), and gallbladder (8). The conclusion that there is a common pathophysiology in diseases of the upper gut may indeed be the basis for a unified concept of pathogenesis (Fig. 1).

In an attempt to assess this hypothesis of a unified concept, one need only refer to Stremple et al (6), who preferred to call the stress ulcer syndrome "acute gastrointestinal focal necrosis syndrome." Their diagram demonstrates that the vasoconstriction responsible for the pathology is mediated through the autonomic nervous system (Fig. 2). As to the liver, Das, Nussbaum, and Leff (9) stated that the hemodynamic changes in the genesis of altered hepatic function can be attributed to physiological processes which result in low oxygen tension and constriction of the mesenteric vessels, due to increases in endogenous norepinephrine.

Despite Silen's observations that "the classical surgical method of inducing pancreatitis by the introduction of bile into the pancreatic duct has held back knowledge to a significant degree" (1), this method remains the experimental choice in demonstrating the pathophysiology of acute pancreatitis. However, Dos Reis (10) in 1963 produced hemorrhagic pancreatitis experimentally in dogs, not only by the intraductal route of bile and trypsin, but also by the injection of trypsin into the splenic vein as well as the carotid artery. Recently, Pantoja et al (11) injected the venom from the scorpion *Buthus quinquestriatus* intraarterially and concluded that the pathologic process is independent of any effect of venom on the papillary muscle tone. Experimental interference with the circulation of the pancreas as conducted by Popper, Nechles, and Russell (12), by Pfeffer and his associates (13), and by Anderson (14) has important inferences. Donaldson et al (15), Broe et al (16), and Studley and Schenk (17) emphasized that it is the ischemia in the microcirculation of the pancreas that is the primary cause of injury to that organ. Goodhead (18) further demonstrated that the vasoconstriction was not limited to the pancreas, since he charted the diminished blood flow in the stomach, duodenum, jejunum, and colon (Fig. 3). Chiu (19) also described a redistribution of blood flow with marked "congestive hypoperfusion" in epithelial lesions of the gastrointestinal tract, kidney, gallbladder, and lung in low-flow states.

Clinically, Warshaw and O'Hara (20) in 1978

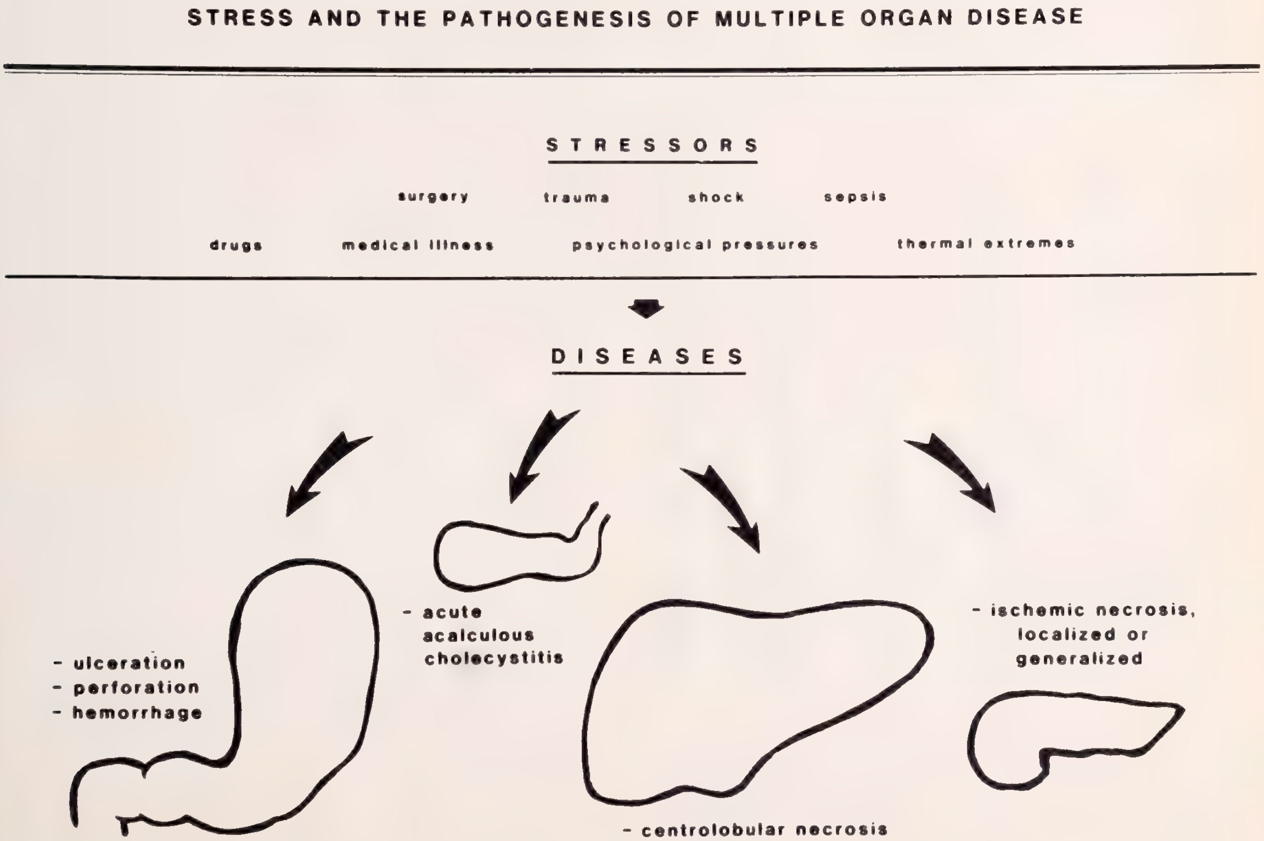
STRESS AND THE PATHOGENESIS OF MULTIPLE ORGAN DISEASE
STRESSORS
surgery
trauma
shock
sepsis
drugs
medical illness
psychological pressures
thermal extremes
DISEASES
- ulceration
- perforation
- hemorrhage
- acute acalculous cholecystitis
- centrolobular necrosis
- ischemic necrosis, localized or generalized

Fig. 1.

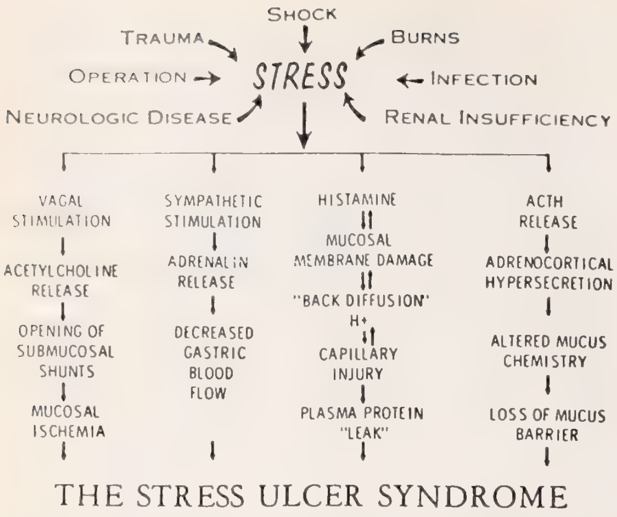
SHOCK
TRAUMA
BURNS
OPERATION
STRESS
INFECTION
NEUROLOGIC DISEASE
RENAL INSUFFICIENCY
VAGAL STIMULATION
ACETYLCHOLINE RELEASE
OPENING OF SUBMUCOSAL SHUNTS
MUCOSAL ISCHEMIA
SYMPATHETIC STIMULATION
ADRENALIN RELEASE
DECREASED GASTRIC BLOOD FLOW
HISTAMINE
MUCOSAL MEMBRANE DAMAGE
"BACK DIFFUSION"
H+
CAPILLARY INJURY
PLASMA PROTEIN "LEAK"
ACTH RELEASE
ADRENOCORTICAL HYPERSECRETION
ALTERED MUCUS CHEMISTRY
LOSS OF MUCUS BARRIER
THE STRESS ULCER SYNDROME

Fig. 2. Major theoretical mechanisms that have been implicated in the pathogenesis of the stress ulcer syndrome. Reproduced with permission from Stremple JF et al. The stress ulcer syndrome. In: Ravitch MM et al, eds. Current problems in surgery. Copyright 1973 by Year Book Medical Publishers, Inc., Chicago.

noted that shock from whatever cause, cardiogenic, anesthetic, or hemorrhagic, increases the susceptibility of the pancreas to destruction. Pancreatic ischemia due to hypoperfusion alone may be the critical factor, according to these authors, even in the absence of shock.

Poon-King, (21), whose interest was in myocarditis resulting from the sting of the scorpion *Tityus trinitatis,* reported elevations of serum amylase in 28 of 45 patients and the diagnosis of acute pancreatitis in 6, or 13%. Cobo et al (22) described the low-flow state in 33 cases of acute pancreatitis. Of these, 29 were due to alcohol, one to trauma, one to calculus cholecystitis, one to acalculus cholecystitis, one to hyperlipidemia.

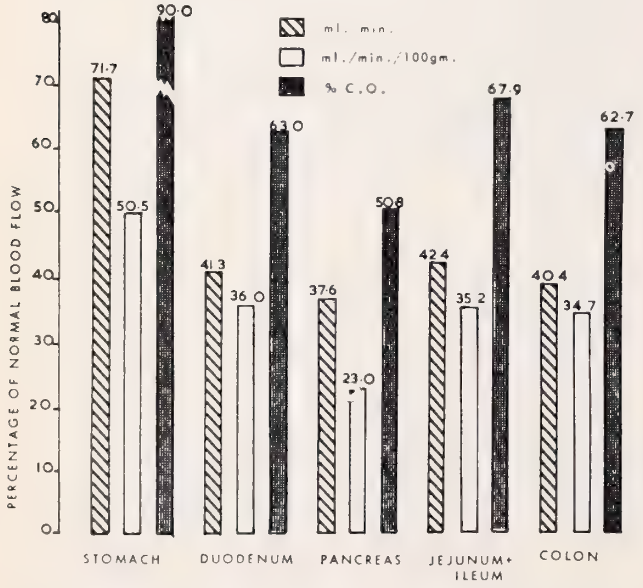

Fig. 3. Mean blood flow to organs expressed as a percentage of the normal flow in the stomach, duodenum, pancreas, jejunum, ileum, and colon in dogs with hemorrhagic pancreatitis. Reprinted by permission of *Surgery, Gynecology & Obstetrics* from Goodhead B. Acute Pancreatitis and Pancreatic Blood Flow. Surg Gynecol Obstet 1969; 129:331–340.

If then the low-flow state is responsible, how is it mediated? Claude Bernard (23), Walter B. Cannon (24), and the late Hans Selye (25) have taught us the importance of the *milieu interieur,* the autonomic nervous system, the adrenal secretions, and finally, the hypothalamic pituitary-adrenal axis. The nonspecific effect of the various stressors accordingly has a common channel, the neurohumoral system. Its excitation results in splanchnic nerve. Gilsdorf et al (30) in 1965 exemia, and hypoxia.

The modus operandi of the evolution of neural, humoral, and vascular effects is not completely understood. Brodie (26) in 1814 described the important role of the central nervous system in the structure and function of the gastrointestinal tract. Pavlov (27) in 1902 provided experimental evidence in scientifically documenting such influence. French (28) has written extensively on the role of the brain in visceral disease. More specifically, Mallet-Guy (29) in 1944 demonstrated that acute pancreatitis could be produced in anesthetized guinea pigs by stimulation of the left splanchnic nerve. Gilsdorf et al (30) in 1965 experimentally enhanced the development of a hemorrhagic or lethal necrotizing pancreatitis from a mild, nonlethal, bile-induced disease by bilateral oblation of the anterior hypothalamic areas, and by stimulation of the posterior hypothalamus as well as the celiac ganglion. Despite the many experimental designs, Olympian in concept, the influence of the central nervous system on gastrointestinal physiology remains an enigma, according to Nyhus (31).

In 1955, a hypothesis was proposed that acute pancreatitis might be a disease of adaptation. The basis for this assumption was simply that if ischemic necrosis of the stomach and duodenum could result from emotional stress, similar pathology could be anticipated in the pancreas, since the latter was an anlage of the upper gut, having the same nerve and blood supply (4). In 1956, an inquiry was made regarding the occurrence of acute pancreatitis during the experimental observation of gastrointestinal lesions in behaviorally conditioned monkeys. A personal communication reported that indeed, one case of acute hemorrhagic pancreatitis was observed (32). Porter (33) reportedly felt that psychic factors may precipitate acute pancreatitis. Warwick and Leavett (34) reported relapsing pancreatitis in a six-year-old child who was subject to the strains of severe emotional difficulties between her parents. Gambill (35) in his monograph in 1973 noted that some patients, when unusually tired or under great stress, not uncommonly develop painful attacks of relapsing pancreatitis. The sixteenth-century British physician J. Aubert is quoted as having written (36) that he "once observed in a Noble woman who for some years was perplexed with Convulsions, Epilepsy and Hysterick passion, this having made her yield to Death; the dead Body being opened, the Pancreas was wholly found ill-affected and ulcerated."

It may then be concluded that any stressor or stressors may produce vasoconstriction, ischemia, and hypoxemia, resulting in destruction of the cellular elements of the pancreas. The psyche, with its effect on the endocrines (37), as well as the autonomic nervous system, plays a large part

TABLE

Clinical Etiologies of Acute Pancreatitis

A. Most common associations
   1. Biliary disease (cholelithiasis)
   2. Alcoholism (? genetic factor)
   3. Traumatic-postoperative
   4. Duodenal ulceration
   5. Idiopathic

B. Infections
   1. Mumps
   2. Coxsackie viruses B_2, B_3, B_5
   3. Hepatitis viruses
   4. *Salmonella typhi*
   5. Group A streptococci (scarlet fever)
   6. Staphylococci
   7. Enteroviruses: echovirus 6, 11, 22, 30
   8. Miliary tuberculosis, actinomycosis
   9. *Candida albicans*
   10. ? Role of *E. coli* in "biliary" group

C. Infestations
   1. Ascaris
   2. Hydatid cyst
   3. *Clonorchis sinensis*
   4. ? *Giardia lamblia*

D. "Metabolic-nutritional"
   1. Hypercalcemia
      a. Hyperparathyroidism (especially perioperative)
      b. Multiple myeloma-lymphoma
      c. Bone metastases
      d. Hypervitaminosis D
      e. Tumors producing PTH-like hormones
   2. Hyperlipoproteinemias, Types I, IV, V
   3. Hereditary
      $\left.\begin{array}{l}\pm\text{leukopenia}\\ \pm\text{thrombocytopenia}\\ \pm\text{aminoaciduria}\end{array}\right\}$ Several variations
   4. Hemochromatosis-hemosiderosis
   5. Cystic fibrosis
   6. Kwashiorkor
   7. Pregnancy–oral contraceptives
   8. "Sprue"
   9. Postgastrectomy malnutrition
   10. Weber-Christian disease
   11. Obesity (? hyperlipoproteinemia, diabetes)
   12. Whipple's disease
   13. Uremia
   14. Postrenal transplant (? immunosuppression)
   15. Postextracorporeal circulation

E. "Mechanical"
   1. Periampullary stone impaction
   2. Carcinoma of pancreas
   3. Metastatic carcinoma to pancreas
   4. Postsurgical (e.g., biliary, sphincterotomy)
   5. Periampullary diverticula
   6. Ascaris
   7. Pressure injuries (e.g., X-ray procedures)
   8. Afferent loop obstruction
   9. Superior mesenteric artery syndrome
   10. Crohn's disease, duodenal
   11. Congenital anomalies (e.g., annular pancreas)
   12. Polyposis, Peutz-Jeghers syndrome
   13. Dystonic sphincter, "papillitis"
   14. Postendoscopic pancreatography

F. Drugs
   1. Corticosteroids, ACTH
   2. Isoniazid
   3. Anticoagulants
   4. Diuretics, especially thiazides
   5. Thiouracil
   6. Oral contraceptives
   7. Furosemide
   8. Azathioprine
   9. Toxins
      a. Methanol
      b. Zinc
      c. Cobalt
      d. Saccharated iron oxide
      e. Mercuric chloride

G. Venom
   1. Scorpion, *T. trinitatis*

H. Vascular
   1. Myocardial infarction—atheromas
   2. Mesenteric infarction
   3. Collagen vascular disease
      a. Polyarteritis
      b. Disseminated lupus erythematosus
   4. Diabetic coma
   5. Eclampsia
   6. ? Electric shock

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in disease as well as in healing (38–41). It is mandatory that psychological factors be added to the important etiologies of acute pancreatitis (Table).

Although disease may have a single etiology, more often it is multifactorial. The pancreas, with its generous supply of blood, nerves, and endocrine glands, may be considered a prime target organ in any systemic insult. Destruction of its tissue causes pain and physical and emotional derangements which, if not recognized early, may lead to further damage of the gland as well as to the production of many noxious peptides. The result is harmful sequelae to other principal organs, namely kidney, lung, liver, heart, and brain.

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Enteropancreatic Reflexes 2. The Effect of Jejunal Distension

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White and Magee (1, 2) demonstrated that the distension of the stomach led to increased pancreatic volume and protein production due to a gastropancreatic reflex, vagally mediated. Sum and Preshaw (3) reported that balloon distension of the duodenum in conscious dogs increased gastric acid secretion but had no effect on exocrine pancreatic secretion.

The role of the small bowel in hormonal regulation of pancreatic secretion is well established (4–6). No data is available about the relation between mechanical stimuli of the small bowel and pancreatic secretion.

The present study reports the effects of jejunal distension on exocrine pancreatic secretion in conscious dogs. An attempt has been made to demonstrate enteropancreatic reflexes.

Materials and Methods

Ten adult mongrel dogs, weighing 15–20 kg, were prepared with Thomas cannulas (7) in the duodenum after preliminary ligation of the accessory pancreatic duct. At the same time, a 12-cm segment of jejunum taken 15 cm distal to the ligament of Treitz was defunctionalized, forming a Thiry loop, with the proximal end closed intraperitoneally and the distal opening exteriorized through the abdominal wall. Secretory tests were commenced two weeks after surgery. The animals were trained to stand quietly without sedation. Each observation was carried out with the animals in the conscious state, deprived of food but not water for at least 24 hours. The canines were studied no more than twice a week and never on consecutive days. A continuous intravenous infusion of 0.45% of sodium chloride was maintained throughout each experiment at a rate of 50 cc per hour to allow for fluid losses. The effect of distension of the jejunal loop on pancreatic secretion was studied under basal and secretin-stimulated conditions.

Pancreatic secretion was collected by direct cannulation of the main pancreatic duct under direct vision through the Thomas cannula at 30-minute intervals in basal conditions and at 5-minute intervals in the secretin-stimulated experiments. Secretin (The Boots Company Ltd.) was used in dosages of 0.03 units per kg per minute. When a plateau had been reached, distension was produced by inserting a Foley catheter in the loop of jejunum through the opening in the abdominal wall. The balloon was inflated with 25 cc of air. The distension of the loop with this amount of air was previously verified under fluoroscopy in each dog. In no experiment did this distension cause pain. After two to three collections, the balloon was released and new samples were taken immediately thereafter.

In a separate group of experiments the effect of jejunal distension on secretin-stimulated secretion was studied after intravenous administration of atropine (1 mg), β blockers (propranolol 0.25 mg/kg), α blockers (phentolamine 0.25 mg/kg) and topical application of 2% lidocaine (20 ml) to the jejunal mucosa. In each experiment, there was a 10-minute interval between the administration of each drug and the distension of the jejunal loop. Jejunal distension was always checked fluoroscopically.

Each sample of pancreatic secretion collected was analyzed individually for volume, bicarbonate and protein concentrations, the latter serving as a measure of enzyme secretion. Bicar-

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bonate was measured with a Beckman Cl/CO_2 analyzer and protein determinations were performed as described by Preshaw and associates (8). Statistical significance was determined by Student's *t* test on the basis of paired observations of control values and values following jejunal distension with and without the drugs used on each dog.

Results

Basal Secretion. Jejunal distension (Fig. 1) did not stimulate pancreatic secretion but resulted in a reduction of 70% in volume from 1.0 ± 0.2 ml to 0.3 ± 0.1 ml ($p < 0.01$). After release of the balloon, secretion returned to basal levels. Mean bicarbonate concentration decreased from 25 mEq/L to 5 mEq/L after distension.

Secretin Stimulation. Pancreatic flow in response to submaximal doses of secretin (0.03 u/kg/min) was reduced 43% ($p < 0.01$) beginning immediately after jejunal distension (Table 1). While bicarbonate concentration (Table 2) was reduced 12% ($p < 0.01$), the bicarbonate output was decreased by 48% ($p < 0.01$). After releasing the balloon, both concentration and output returned to basal levels (Fig. 2).

The secretory rate following atropinization was not affected by jejunal distension (Fig. 3). Intravenous atropine (1 mg) blocked the inhibitory effect of jejunal distension on both flow and bicarbonate concentration (Tables 1, 2).

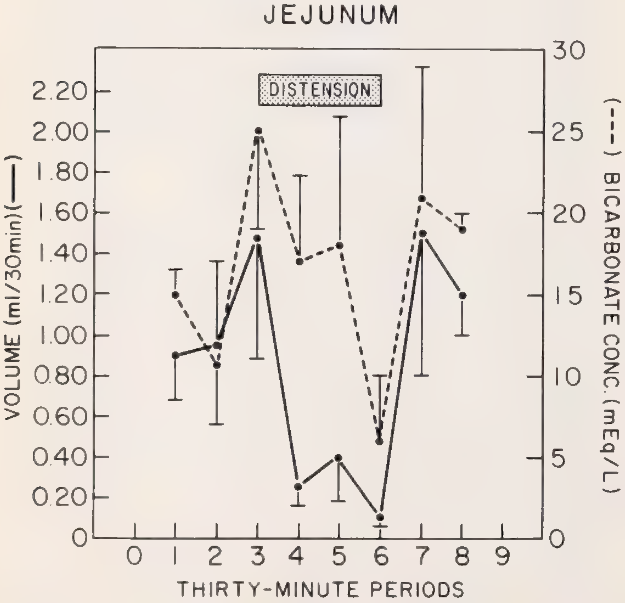
The inhibitory effect of jejunal distension was also blocked by topical applications of lidocaine 2% to the jejunal mucosa. Both flow and bicarbonate secretion were unchanged (Tables 1, 2). Propranolol and intravenous phentolamine did not block the inhibitory effect of jejunal distension. A similar pancreatic response was obtained with and without these drugs: decrease from 43% to 47% in volume (Table 1) and 7% to 12% in bicarbonate concentration (Table 2), both statistically significant ($p < 0.01$). After the release of the balloon, volume and bicarbonate returned to normal levels (Figs. 4, 5).

Enzyme Response. The enzyme data (Table 3) showed that protein concentration was not significantly affected by jejunal distension. The rate of protein secretion was inhibited 45%. Topical lidocaine abolished the inhibitory effect of distension. Propranolol and phentolamine did not interfere with the inhibitory effect of distension.

Discussion

These results clearly demonstrate that mechanical distension of the jejunum inhibits pancreatic exocrine secretion. Volume, bicarbonate output, and protein secretion were markedly and significantly reduced. The pancreatic inhibition was observed in all experiments within 5 minutes following distension. Release of distension was followed immediately by return to predistension levels.

This is the first demonstration of an inhibition of pancreatic secretion by mechanical stimulation in the proximal small intestine. Other studies have shown inhibition (9–11) of pancreatic secre-



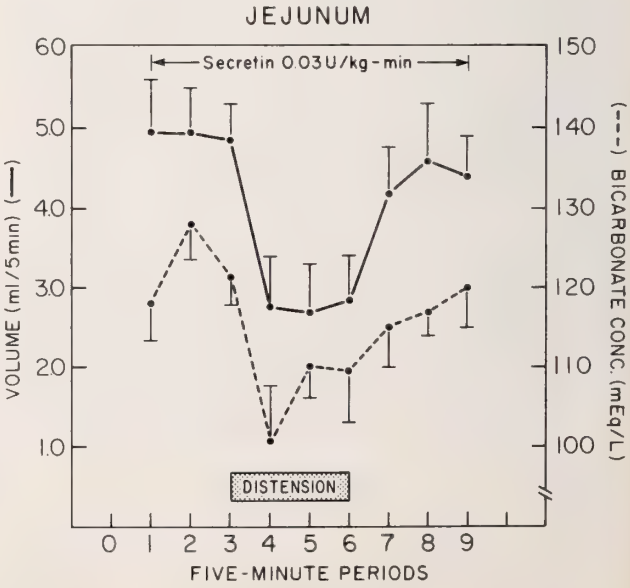


Fig. 1. Left Effect of jejunal distension on basal pancreatic flow and bicarbonate concentration.

Fig. 2. Right Effect of jejunal distension on secretin-stimulated flow and bicarbonate concentration.

TABLE 1

Effects of Jejunal Distension on Pancreatic Flow

	No. exp.	ml/5 min Control Mean ± SE	 Distension Mean ± SE	% Change
Secretin	33	4.9 ± 0.34	2.8 ± 0.38*	−43
Secretin with IV atropine	38	2.4 ± 0.14	2.5 ± 0.11	+4
Secretin with topical lidocaine	26	3.9 ± 0.18	3.6 ± 0.26	6
Secretin with IV propranolol	25	4.4 ± 0.18	2.5 ± 0.18*	−43
Secretin with IV phentolamine	14	5.4 ± 0.25	2.8 ± 0.26*	−47

* $p = 0.001$.

tion following infusion of fatty acids into the lumen of the distal small bowel and colon. Harper (12) demonstrated this inhibitory effect on volume, bicarbonate, and enzyme secretion in anesthetized cats with pancreatic denervation. Cross-circulation studies in the rat have shown that intraileal oleic acid infusion produces inhibition of pancreatic enzyme secretion in the recipient animal. A polypeptide material obtained from ileal mucosa has been claimed to be responsible for this inhibitory effect (13).

In proximal small bowel, infusion of fatty acid results in a delayed inhibition of pancreatic secretion (14). Enteroglucagon is known to be released by fatty acids and by parasympathetic stimulation, in humans and dogs (14), a release inhibited by atropine (15). Dyck (16) found that hypertonic glucose infusion in the jejunum inhibited the bicarbonate flow and enzyme pancreatic secretion in humans, an inhibition correlated with increased circulating immunoreactive glucagon. The same study reports inhibition of volume and bicarbonate output of the pancreatic secretion by pancreatic glucagon derived in humans from the alpha islet cells and in dogs from similar cells found in the oxyntic gland area of the stomach (17, 18). In fact, glucagon-like immunoreactivity (enterglucagon) is widely distributed throughout the mucosa of the gastrointestinal tract (19), but its biological activity is very weak. Thus, there is no convincing evidence that the inhibitory effect of the jejunal distension on pancreatic secretion is mediated by the release of glucagon or any other glucagon-like peptide.

Pancreatic polypeptide (PP) inhibits secretion of pancreatic juice and particularly of pancreatic enzymes both in the basal and secretin-CCK-stimulated secretion (20). A biphasic action on water-bicarbonate, augmentation followed by inhibition, has been shown following stimulation by secretin alone (20). The pancreas has approximately 93% of the total pancreatic polypeptide in the gut (21). Although PP is detectable throughout the entire intestinal tract of the primate, its concentration is much less in the jejunum than in the pancreas (21). Plasma from patients who have undergone total pancreatectomy has no detectable PP postprandially, suggesting that the pancreas is the main source of the peptide in the circulation (22). Release of PP is blocked by truncal vagotomy for several months (22), but vagal stimulation is not the only mechanism of PP release. In the isolated perfused canine pancreas, cerulein, glucose-dependent insulin-releasing polypeptide (GPI), vasoactive intestinal peptide (VIP), gastrin, and acetylcholine all produce significant increases in perfusate PP concentration (23).

Some degree of cholinergic tone appears to be essential for maintaining basal secretion of PP and for the response to gut hormones. The inhibitory response of flow and bicarbonate after jejunal distension differs from the pattern produced by PP, in which enzyme concentration as well as flow are diminished. In this study, systemic atropine blocked the inhibitory effect of jejunal distension at the same time it blocked the release of PP. Thus, the results suggest that a release of PP is not responsible for the inhibition following jejunal distension.

Atropine-induced smooth-muscle relaxation of the bowel might interfere with the mechanical stimulation of jejunal distension. However, fluoroscopic examination during the test runs did not show change.

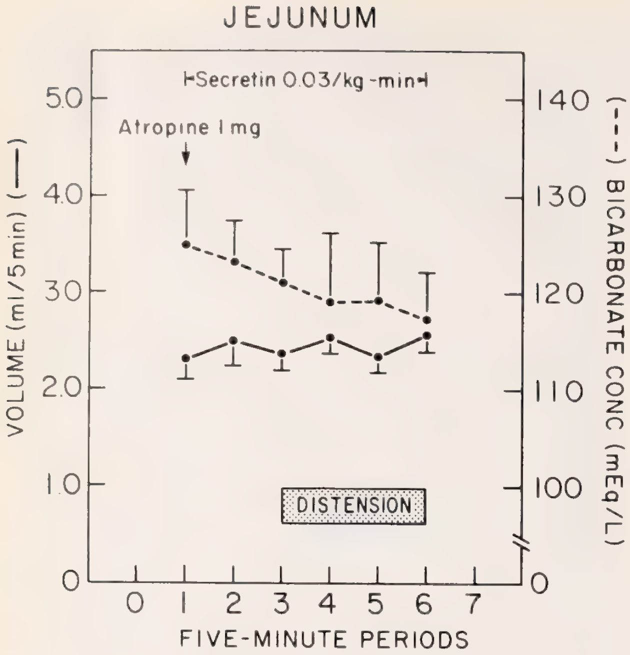
Tension receptors in the muscular wall of the

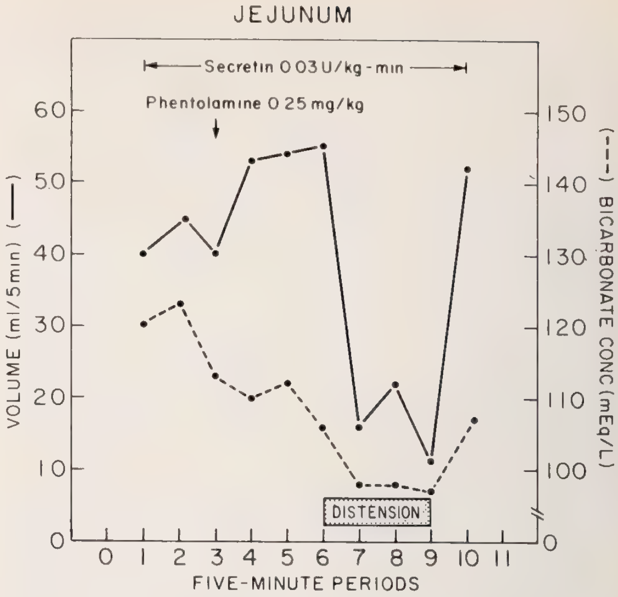
TABLE 2

Effects of Jejunal Distension on Pancreatic Bicarbonate Concentration and Output

	No. exp.	Concentration (mEq/L) Control	 Distension	 % Change	 Control	Output (mEq/5 min) Distension	 % Change
Secretin	33	123 ± 2.8	108 ± 3.8*	−12	0.60 ± 0.04	0.31 ± 0.04*	−48
Secretin with IV atropine	37	123 ± 2.8	119 ± 3.5	−46	0.29 ± 0.01	0.29 ± 0.01	0
Secretin with topical lidocaine	26	121 ± 2.9	112 ± 3.5	−7	0.49 ± 0.02	0.41 ± 0.03*	−16
Secretin with IV propranolol	25	109 ± 2.7	101 ± 2.4*	−6.7	0.46 ± 0.02	0.25 ± 0.02	−40

* $p < 0.01$.





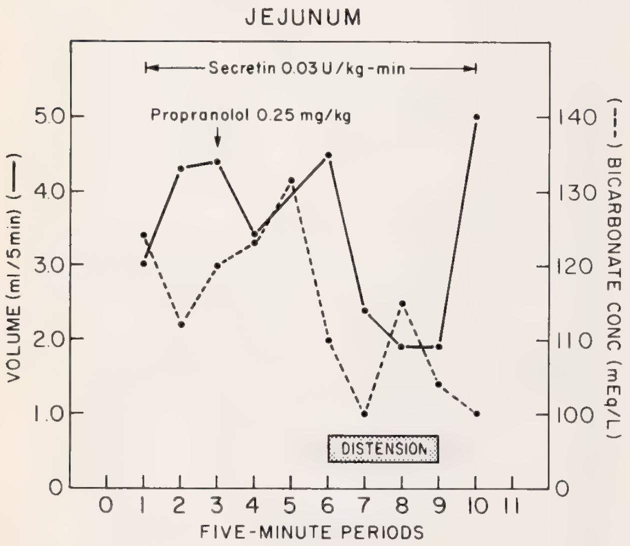


Fig. 3. Top left Effect of atropine on pancreatic response to secretin-stimulated secretion after jejunal distension.

Fig. 4. Bottom left Effect of propranolol on pancreatic response to secretin-stimulated secretion after jejunal distension.

Fig. 5. Top right Effect of phentolamine on pancreatic response to secretin-stimulated pancreatic secretion after jejunal distension.

jejunum initiating afferent impulses in the vagus have been demonstrated in cats (24). The blocking effects of the pancreatic inhibition by topical lidocaine suggests the presence of this type of receptor in the jejunal mucosa. The stimulus used in the present study (distension) can elicit a reflex blocked by atropine, suggesting a cholinergic mediation. Previous studies have shown the existence of vagally mediated gastropancreatic and pyloropancreatic reflexes (1, 25). Furthermore, it has recently been suggested that long vasovagal reflexes are responsible for the majority of the exocrine pancreatic response to intraluminal stimulation in the gut by amino acids and lipids (26). Catecholamines do not seem to play any role in this effect, since the adrenergic blocking agents did not affect the inhibition of the pancreatic secretion during jejunal distension.

Summary

The inhibitory effect of the jejunal distension on pancreatic secretion shown in this study can

TABLE 3

Effects of Jejunal Distension on Pancreatic Enzyme Protein Concentration and Output

		Concentration (mg/ml)			Output (mg/5 min)		
	No. exp.	Control Mean ± SE	Distension Mean ± SE	% Change	Control Mean ± SE	Distension Mean ± SE	% Change
Secretin	11	8.5 ± 0.51	7.6 ± 0.85	−12	41.0 ± 3.91	22.5 ± 3.22	−45
Secretin with IV atropine	13	7.1 ± 1.16	6.8 ± 1.01	−5.2	16.6 ± 2.98	17.6 ± 2.91	+6
Secretin with topical lidocaine	9	7.5 ± 0153	8.0 ± 0.91	+7.7	31.1 ± 4.22	30.8 ± 7.75	+1
Secretin with IV propranolol	10	9.7 ± 0.73	7.5 ± 0.79	−23	43.7 ± 3.98	19.9 ± 4.18	−46
Secretin with IV phentolamine	6	8.7 ± 0.65	5.9 ± 0.80	−33	44.9 ± 6.28	18.5 ± 4.68	−59

be explained by atropine-sensitive reflexes, probably vagally mediated. The presence of local reflexes and the participation of hormonal mediation in this phenomenon require further investigation.

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The Effect of Age on Human Exocrine Pancreatic Secretion

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Age-related changes in the structure and function of the gastrointestinal tract have been the subject of many publications (1–3). There is a consensus that basal and stimulated gastric secretion declines with age (4). Studies of pancreatic secretion in the elderly are scattered in the old literature and are rather controversial.

Previously published data from this laboratory indicated that age and sex have little or no influence upon the secretory responses of the human pancreas to a standard dose of secretin (3). Almost 20 years have passed since this publication. The present report is a retrospective analysis of the observations gathered over this period.

Material and Methods

Routine secretin tests were performed according to a previously described method (5). Pancreatic secretion was stimulated with an intravenous bolus injection of secretin (Boot) 1 unit per kg. The duodenal aspirate was collected by intermittent suction through a double lumen tube which separated gastric and duodenal fluids. The duodenal collections were analyzed for volume (in ml/kg), bicarbonate, and protein concentrations. The pH of gastric content was also measured. The amylase activity of blood drawn before secretin injection is analyzed in the present study.

The results of secretin tests performed on 2,352 patients are reported in three main groups, each stratified with respect to age as follows: 50–59 years, 60–69 years, 70–79 years, >80 years.

The first group, 1,615 patients, combines those in whom either organic disease or pathological involvement of the pancreas was excluded after thorough clinical observation, appropriate diagnostic tests, or postmortem examination.

In the second group are the 381 patients diagnosed as having chronic pancreatitis. The diagnosis was established on the basis of typical history and clinical presentation, and in some of the patients by the characteristic ERCP picture or the histologic appearance of the pancreatic specimen taken during laparotomy or at autopsy. Results of secretin tests in all of these patients indicated pancreatic exocrine insufficiency.

In the third group are the 356 patients in whom diagnosis of pancreatic cancer was confirmed histologically after an operation or autopsy.

The normal ranges and means of the standard secretin test (Table 1) were established for this laboratory on the basis of results of secretin tests performed on 300 healthy subjects aged 20 to 40 years. The present data were evaluated using unpaired Student's *t*-test.

Results

In the first group, patients without pancreatic disease, the mean values of the volume of secretin secreted and bicarbonate concentration were the same as for healthy young (20–40-year-old) subjects and for all four age groups. The mean value of amylase secretion, although well in the range accepted as normal for this laboratory (8.0–36.0 u/kg), was statistically ($p < 0.001$) lower in the

TABLE 1
Secretin Test Data: Normal Ranges and Means, 300 Healthy Controls

	Duodenal			Blood amylase (IU)
	Volume (ml/kg)	HCO_3 (mEq/l)	Amylase (u/kg)	
Range	2.0–4.4	90–130	8.0–36.0	60–180
Mean ± SD	3.2 ± 0.6	110 ± 10	22.0 ± 7.0	120 ± 30

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TABLE 2

Secretin Test Data: Patients without Pancreatic Disease, by Age Decade

Age range (yrs)	F:M/Total No.	Age (yrs)	Duodenal (mean ± SD)			Blood amylase (IU)	Gastric (mean ± SD)	
			Volume (ml/kg)	HCO_3 (mEq/l)	Amylase (u/kg)		ph	% pts pH < 3.5
50–59	469:300/769	54 ± 3	3.5 ± 1.2	109 ± 12	17.0 ± 7.9	76 ± 33	3.5 ± 2.3	64
60–69	352:291/643	64 ± 3	3.5 ± 1.1	109 ± 13	17.0 ± 7.6	68 ± 30	3.7 ± 2.4	60
70–79	108:80/188	73 ± 3	3.5 ± 1.2	109 ± 14	22.8 ± 12.9	77 ± 37	4.4 ± 2.6	50
>80	4:11/15	83 ± 3	3.4 ± 1.0	105 ± 19	19.4 ± 10.7	69 ± 39	4.4 ± 2.1	47

patients in their fifties and sixties than in those aged between 20 and 40 years.

Mean values of blood amylase activity were about 70 IU in all four age groups, that is, just above the lower limit of the norm, but significantly ($p < 0.001$) below the normal mean value for a young population (120 IU).

The mean pH of the gastric content increased from 3.5 in the group aged 50–59 years to 4.4 in the group aged 70–80 years ($p < 0.001$). Furthermore, the percentage of patients with gastric-content pH of 3.5 or less declined with age (Table 2).

The most prominent change in the results of secretin tests in the second group, patients with chronic pancreatitis, is a low bicarbonate concentration in the duodenal aspirate (Table 3), a pattern characteristic for chronic pancreatitis. The data are similar for the three age groups under 80 years. Changes noted in patients aged over 80 years are not significant because of the small sample. In these patients, as in those without pancreatic disease, serum amylase concentrations were significantly decreased. The changes in basal gastric pH were similar with aging to those observed in patients without disease of all ages, that is, there was a significant increase in pH and a decrease in percentage of free acid with age.

In the third group, patients with carcinoma of the pancreas (Table 4), the characteristic secretory pattern of decreased flow and enzyme concentration after secretin is evident. The secretory parameters of volume, bicarbonate concentration, and amylase secretion did not change in patients aged 50–79 years. The size of the sample of patients over 80 years of age is too small for comparison.

Blood amylase activity in patients with pancreatic cancer did not change significantly over the decades, but it was statistically less than observed in healthy young controls. Unstimulated gastric pH rose and the percentage of patients with free acid, <pH 3.5, declined with age.

When the secretin test data of pancreatic cancer patients in age groups 50–59 years, 60–69 years, and 70–79 years were analyzed by site of tumor (Table 5), patients with cancers of the head and body evinced findings similar to those for patients with pancreatic cancer regardless of site. The data for patients with cancers of the tail were not significantly different from those for patients without pancreatic disease.

Discussion

The analysis of the data indicates that in persons who show no evident pathological process involving the pancreas, exocrine secretion of the pancreas is well preserved for flow and bicarbonate and does not change with age up to the eighth decade of life. Similarly, aging does not seem to influence typical patterns of pancreatic secretion in patients with chronic pancreatitis or

TABLE 3

Secretin Test Data: Patients with Chronic Pancreatitis, by Age Decade

Age range (yrs)	F:M/Total No.	Age (yrs)	Duodenal (mean ± SD)			Blood amylase (IU)	Gastric (mean ± SD)	
			Volume (ml/kg)	HCO_3 (mEq/l)	Protein (u/kg)		pH	% pts pH < 3.5
50–59	91:111/202	54 ± 3	3.1 ± 1.5	59 ± 19	8.6 ± 6.6	60 ± 30	3.4 ± 2.4	51
60–69	54:78/132	64 ± 3	3.2 ± 1.5	58 ± 18	8.8 ± 6.8	50 ± 26	3.7 ± 2.4	61
70–80	19:23/42	74 ± 2	3.3 ± 2.0	64 ± 25	17.1 ± 17.3	64 ± 31	4.4 ± 2.8	52
>80	2:3/5	84 ± 3	2.3 ± 0.9	70 ± 8	12.2 ± 9.4	81 ± 34	5.4 ± 2.5	20

TABLE 4

Secretin Test Data: Patients with Pancreatic Cancer, by Age Decade

			Duodenal (mean ± SD)				Gastric (mean ± SD)	
Age range (yrs)	F:M/Total No.	Age (yrs)	Volume (ml/kg)	HCO_3 (mEq/l)	Amylase (u/kg)	Blood amylase (IU)	pH	% pts pH < 3.5
50–59	49:69/111	55 ± 3	1.4 ± 0.6	86 ± 29	6.9 ± 6	65 ± 35	3.7 ± 2.5	66
60–69	74:87/161	64 ± 3	1.4 ± 0.7	85 ± 26	7.1 ± 5.6	57 ± 31	3.7 ± 2.4	56
70–79	21:54/75	74 ± 3	1.4 ± 0.8	79 ± 27	7.0 ± 6.0	58 ± 34	4.0 ± 2.6	52
>80	3:6/9	82 ± 2	1.1 ± 0.4	62 ± 20	3.6 ± 3.3	70 ± 18	3.8 ± 1.9	67

TABLE 5

Secretin Test Data: Patients with Pancreatic Cancer, by Location of Tumor

			Duodenal (mean ± SD)			
Site of Ca Pancreas	F:M/Total No.	Age (yrs)	Volume (ml/kg)	HCO_3 (mEq/l)	Amylase (u/kg)	Blood amylase (IU)
Body, head, and tail	140:216/356	64 ± 7	1.4 ± 0.7	84 ± 24	6.9 ± 5.9	60 ± 33
Body and head	126:196/322	64 ± 8	1.2 ± 0.5	81 ± 27	6.2 ± 5.0	60 ± 32
Tail	13:20/33	63 ± 7	2.7 ± 0.8	101 ± 7	14.4 ± 8.2	55 ± 17

carcinoma of the pancreas. The secretion of enzyme following secretin in persons in their fifties, sixties, and seventies was consistently lower than that observed in young healthy controls. Serum amylase concentrations also were statistically lower than those observed in healthy young controls in all age groups, with or without pancreatic disease.

Many studies indicate that gastric secretion decreases with age (4, 6). In this series, gastric secretion was not directly studied, but a statistically significant age-related increase of basal gastric pH was noted.

The percentage of patients with low (3.5 and below) gastric pH decreased gradually with age. In a recent study, Kekki et al (6) reported the incidence of gastritis increased with age and was accompanied by a significant decrease in acid output. On the other hand, there was no acid output decrease with age in subjects with morphologically normal mucosa. Kreel and Sandin (7) reported autopsy findings indicating pathologic lesions such as fibrosis and atrophy in the pancreas with increasing age. Bartos and Groh (8) noted that in older people, a pancreas subjected to repeated stimulation exhibits diminished exocrine response. This suggests that although the functional capacity of the pancreas appears to be relatively preserved, its reserve is diminished with aging. The present retrospective study confirms the preservation of secretory capacity for fluid and bicarbonate but a loss of enzyme secretion. The significant decreases in serum amylase concentration with aging are consistent with the diminished enzyme secretion noted. Meyer et al (9) did not note an age-related change in serum amylase. These disparate findings require further study because of implications for the criteria governing the diagnosis of acute pancreatic inflammations in the aged.

Summary and Conclusions

A retrospective study of data from 2,352 secretin tests showed a preservation of pancreatic secretory capacity for flow and bicarbonate secretion but not for enzyme secretion, which appeared to be statistically diminished in the decades 50–59, 60–69, 70–79. The sample of patients aged >80 years was insufficient for analysis.

Characteristic secretory patterns for pancreatic inflammation and pancreatic cancer are maintained with age.

The data show an age-related increase in gastric pH as well as an age-related decrease in the incidence of free gastric acidity.

The mean serum amylase concentration in the later decades of life was significantly lower than that observed in healthy younger patients. If these findings are confirmed, criteria for the diagnosis of acute pancreatitis in the aged require revision.

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The Natural History of Alcoholic Pancreatitis: Update 1985

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The natural history of alcoholic pancreatitis can be divided into 3 stages: latent, acute, and chronic. The latent or initial period is a long silent subclinical interval in which continuous toxic metabolic alcohol pancreatic injury occurs. In those individuals in whom alcoholism is converted into alcoholic pancreatitis, some unknown mechanism induces acute acinar cellular necrosis, resulting in acute alcoholic pancreatitis. With continued alcoholism, recurrent acute and subacute inflammations alternate with attempts at repair until the complications of the inflammatory process result in a number of complications of chronic pancreatitis:

1. pancreatic ascites
2. pancreatic pseudocyst
3. pancreatic abscess
4. peptic hypertension
6. endocrine insufficiency-diarrhea
7. exocrine insufficiency-steatorrhea
8. intractable pain, malnutrition, and drug addiction.

Little was known concerning the pathophysiology of the latent period of alcoholic pancreatitis until the reports of Bordalo et al and Dreiling. The etiopathogenic significance of this period was obscured by the clinical observation that given 100 alcoholics, only 15% will develop clinical cirrhosis, about 5% will develop clinical pancreatitis, and perhaps 1% will develop both cirrhosis and pancreatitis. The remaining 80% are Winston Churchills—yet even this group exhibits lesions in both the liver and the pancreas.

Bordalo, Dreiling, and Noronha pointed out that patients in the latent period demonstrated (a) changes in secretory pattern, (b) electronmicroscopic acinar cell pathology, and (c) vague digestive complaints.

The change in secretory pattern is pancreatic hypersecretion, a pattern which is a characteristic response for a pancreas subjected to repeated minimal injury. At present sufficient data is not available to indicate what percentage of patients in the latent period exhibit hypersecretion. It is postulated that hypersecretion is the initial immediate response to alcoholic injury and that this is accompanied at first by pancreatic hypertrophy and hyperplasia. During the latent period, secretory hypersecretion undergoes a shift through the normal ranges to pancreatic secretory insufficiency, as hypertrophy and hyperplasia give way to parenchymal fibrosis, atrophy, and necrosis.

The electromicroscopic changes observed during the latent period include acinar alterations such as (a) deposition of fat, (b) endoplasmic reticular hyperplasia, and (c) mitochondrial abnormalities. These findings are similar to those seen in the liver of alcoholics and, of course, suggest toxic metabolic processes. Indeed, biopsies taken from the liver and pancreas of a series of patients in the latent period of alcoholism revealed parallelism in the hepatic and pancreatic findings.

Although the latent period is presumed to be one in which the consumption of about 80 gm of alcohol daily is not associated with clinical findings, careful questioning of alcoholics reveals a number of vague digestive complaints: nausea, belching, abdominal discomfort, flatulence, bowel irregularities. Whether these vague symptoms are related to the hepatic and/or pancreatic alterations remains a question to be resolved. Gastritis was considered the culprit in the past.

Why the latent period terminates in an attack

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of acute pancreatitis in some patients, in hepatitis and cirrhosis in others, and continues for a lifetime in the majority of patients is still an enigma. Nor is the factor precipitating acute pancreatitis known. Many years ago, Howard Spiro, an outstanding gastroenterologist, stated that the initial attacks of acute pancreatitis in alcoholics represent an acute exacerbation of chronic pancreatitis. Indeed if alcoholism continues, the secretory pattern typical of chronic pancreatitis, namely low bicarbonate, confirms this opinion.

The natural history of chronic inflammation in the pancreas is dependent upon the pattern of drinking and the pathology resulting from the acute attacks. The clinical possibilities are numerous and diverse. In some, there is a continuous recurrence or acute exacerbation of inflammation, which over the years becomes less severe and more infrequent until the pancreas "burns out" in atrophy and fibrosis. Although pain is almost always present, in some patients it is inexplicably absent. Calcification is a usual, but not an inevitable, result of the longstanding inflammation; cancer is a debatable consequence. Perhaps alcoholics do not survive long enough. In fact, the mortality in chronic alcoholic pancreatitis is significantly higher than in the general population. The end stage is endocrine and exocrine insufficiency.

In alcoholics in whom extensive necrosis occurs, permanent damage to the main ductal systems, parenchyma tissue, and peripancreatic connective tissues manifests itself as ductal calcification, pseudocyst, abscess, pancreatic ascites, portal hypertension, gastric outlet obstruction, obstructive jaundice, and secondary cholelithiasis.

The loss of function resulting from parenchymal necrosis, atrophy, and/or fibrosis replacement produces first of all endocrine insufficiency (diabetes); second, exocrine deficiency (steatorrhea); and third, peptic ulceration.

Banks and Marks have reported the incidence of these clinical manifestations as follows:

diabetes	30%	cirrhosis	5%
jaundice	18%	TB	3%
pseudocyst	15%	gallstones	2%
hemorrhage	10%	pancreatic ascites	1%
steatorrhea	5%	bone necrosis	0.5%

Chronic Massive Pancreatic Ascites. As a complication of chronic pancreatitis, chronic massive pancreatic ascites was recognized as a clinical entity only in the 1960s; it was previously assumed to derive from the liver, especially in alcoholics. Pancreatic ascites is characterized by a syndrome of persistent fever, persistent leukocytosis, persistent hyperamylasemia, persistent pleural and abdominal effusions, recurring signs of peritonitis, marked wasting, and progressive deterioration.

Theoretically, such ascites may derive from the pancreas due to digestive erosion of a main duct, rupture of a pseudocyst, or lymphatic blockade within the pancreas and retroperitoneum. Sonography has not disclosed discrete fluid collections in these cases, but rather, enormous generalized enlargement of the pancreas. In the early cases subjected to surgery, no cysts were encountered. The pancreas presented as a large boggy mass—a Wurst pancreas.

The treatments for massive pancreatic ascites include sphincterotomy, external drainage, internal drainage for pseudocyst, and thoracic duct drainage. Lymphatic blockade appears to be the cause, and the ascites will respond to thoracic duct drainage.

Pancreatic Pseudocyst and Abscess. The complications pancreatic pseudocyst and pancreatic abscess are grouped together since they are related pathogenetically and may be treated similarly. The pathology of acute pancreatitis is characterized by liquefaction necrosis. Microcysts are a normal development. Coalescence to pseudocyst is probably more frequent than previously believed and spontaneous resolution is not uncommon. Many so-called pseudocysts are really collections in a lesser sac blocked by inflammatory closure of the foramen of Winslow. Finally, there exists a range of lesions, from sterile pseudocyst to infected pseudocysts to infected abscess to sterile pancreatic abscess. Abscess might be considered superinfection during development.

The classical approach to pseudocyst is by external drainage to prevent rupture, and mandatory external drainage of abscess is designed to prevent generalized sepsis. Both therapies result in troublesome external pancreatic fistulas which, in themselves, present surgical problems whenever there is cicatricial obstruction in the proximal pancreatic duct.

Thus, excision of pancreatic pseudocysts when feasible due to location in the left pancreas or by internal drainage into a neighboring viscus, most commonly the stomach, has been the treatment of choice. Since 1982, sonographic and computerized tomographic findings have indicated that pseudocysts are much more common following alcohol-induced pancreatitis, and that spontaneous resolution is not infrequent. Indeed, some pseudocysts, and even abscesses, respond to percutaneous aspiration under sonographic control.

Peptic Ulcer. The incidence of peptic ulcer as a complication has been reported in the literature variously as 3.8%–35%. In healthy subjects as well as in patients with uncomplicated peptic ulcer, the peak bicarbonate secretion of the pancreas exceeds the acid secretory capacity of the stomach; but in chronic pancreatitis, bicarbonate output is much diminished and cannot neutralize gastric acid output.

These ulcers respond poorly to antrectomy alone; a vagisection appears to be necessay to overcome the pancreatic factor in pathogenesis and prevent the development of marginal ulcer. Alternate therapy would be H_2 blockers.

Gastroduodenal Obstruction. In patients with chronic pancreatitis, gastroduodenal obstruction is due to inflammatory fibrosis of the juxtapyloric region. Surgical bypass or extensive pyloroplasty, if feasible, will relieve the obstruction. Even in the absence of gastric hypersecretion, vagisection is mandatory to prevent marginal ulceration.

Obstructive Jaundice. In chronic pancreatitis, obstructive jaundice differs from the temporary jaundice due to edema in acute pancreatitis. In patients with the chronic disease, jaundice is due rather to fibrous encasement of the distal common duct as it traverses the pancreas to enter the duodenum. If untreated, cholecystitis, gallstone, cholangitis with gram-negative sepsis, and even biliary cirrhosis may develop.

This serious complication responds neither to cholecystectomy, prolonged choledochostomy, common duct dilatation, nor sphincteroplasty. The long stenotic segment of the intrapancreatic duct must be bypassed.

Portal Hypertension. In chronic pancreatitis portal hypertension may result from the associated hepatic cirrhosis in alcoholics, or thrombosis and fibrous obliteration of an encased splenic vein, or from both factors.

In treatment of life-threatening hemorrhages from varices due to the localized portal hypertension caused by splenic vein obstructions, splenectomy and coronary ligation suffice. When the portal hypertension is due to cirrhosis, the effect of portocaval or mesocaval shunting on the pancreas must be considered. Portocaval and mesocaval shunting decrease the pancreatic volume, bicarbonate, and enzyme secretion. Splenorenal shunting increases these parameters. These data, unexplained at present, may account for the increased incidence of peptic ulcer following shunting and indicate a physiologic basis for preferring the splenorenal decompression when feasible.

Pain. The most challenging complication of chronic pancreatitis is unremitting pain, frequently associated with drug addiction and incapacity for work. It is not clear whether the pain derives from continued subacute pancreatic inflammation, from inflammatory and fibrotic encasement of peripancreatic autonomic nerves and ganglia, from continued retroperitoneal and lymph node inflammation, or from pancreatic secretion against ductal obstruction. Accordingly, surgical measures to combat pain and rehabilitate patients are diverse and meet with indifferent success. The surgical therapies include: operations on the biliary tract, gastrointestinal diversion to splint the pancreas, nerve interruption operations, and procedures directed toward pancreatic pathologies.

Another facet in the history of alcohol-induced pancreatitis is one of personality change, psychoneurosis, frequently leading to drug addiction, a combination which renders clinical assessment difficult and evalution of pain impossible. This association has intrigued modern physiologic psychiatrists who have discarded the simplistic explanation of emotional response transmuting to organic response transmuting to organic disease and postulate, rather, a yet-undiscovered biophysical relationship based on neuroendocrine hormonal inbalance. Another neuropsychiatric phenomenon is the persistence of pancreatic pain even after total pancreatectomy. Poster reported this type of phantom pancreas in half of a series of 21 total pancreatectomies.

The final common pathway of alcohol-induced chronic pancreatitis thus is a combination of

- personality disorder
- diabetes
- malnutrition and malabsorption
- unremitting pain and drug addiction
- shortened life span.

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Preliminary Observations on Application of Ethibloc in Necrohemorrhagic Acute Pancreatitis in Humans

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Abstract

Diminishing the death rate from serious forms of acute pancreatitis remains a challenge, as evidenced by the recurrent failure of multiple therapeutics. In this preliminary report we describe some experimental results of Prolamine in dogs and the first application of this new method to human beings with necrohemorrhagic acute pancreatitis, presenting our observations only as a new possibility for further exploration and research.

In 1982 we came across a German publication dealing with the application of Prolamine as an antialgic treatment to patients suffering from chronic pancreatitis of alcoholic origin, and as a preventive agent against fistulas, which bring about complications in pancreatic-jejunal anastomosis after a duodenopancreatectomy (1, 2). We were quite surprised when we realized that the authors did not report acute pancreatitis as a complication of the method, in spite of its blocking the pancreatic ductal system, since the obstacle in the free drainage of the pancreatic juice is known to be one of the main causes of acute pancreatitis. This absence of complications raised the possibility of some unknown therapeutic action of Prolamine which might prevent the onset of the complications.

In order to prove this hypothesis we started some experimental research, published by the Argentine Academy of Surgery in 1983 (3). We did not find any bibliographic references in the Argentine or world literature; however, David A. Dreiling brought to our attention reports of similar initiatives by groups of researchers in Holland and Germany in summaries of European Pancreatic Club proceedings. In none of them was acute pancreatitis referred to as a complication, and no comments were made as to the possible therapeutic actions of the drug in serious inflammation.

In our first experiment we used chlorine calcium (Cl Ca) in dogs to induce serious acute pancreatitis. We agree with the principle that this is an artificial method of causing serious acute pancreatitis, and reason that if Prolamine does modify the evolution of that condition, inducing the condition and then treating affected animals with the agent might be regarded as eloquent proof of the action of the drug. We started with a control group in which 100% of the animals died before 36 hours. The necropsy of the pancreas revealed injuries of such importance that the death of the animals was inexorable.

The second step consisted of using Cl Ca to induce pancreatitis in 12 dogs and applying Prolamine 20 minutes after induction. Because of the anatomic disposition of the pancreatic ducts, with close confluence to duodenal pores, the catheter was introduced only in the duct which drains the upper lobe of the gland, thus restricting the pancreatitis to that sector; the caudal lobe remained unaffected. In this group of Prolamine-treated dogs, the mortality caused by Cl Ca within 36 hours was 8.6%, compared with 100% mortality in the untreated control group. One of the ani-

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mals died on the 4th day, bringing total mortality to 17.4% for the longer period.

These results supported expectations of Prolamine, although without a theoretical foundation. We have outlined a hypothesis as to its possible action: when penetrating the internal pancreonal unity, and once solidified, the Prolamine would block the exocrine pancreatic function, working upon the cellular and intercellular structures injured by the aggressive agent. It would act at the same time upon the sound cellular and intercellular elements which were obstructed by the drug as well. All this could prevent the activated enzymatic passage into the interstice, thus restraining the physiopathologic process.

Adaptation to Clinical Use. We then tried to transform the pancreatic gland of a new group of animals into a gland similar to the human gland ("humanization of dog pancreas") so as to apply the results of the experiment to patients suffering from serious acute pancreatitis (4). The research was now geared toward fast adaptation to a future clinical stage, since in Europe the use of the drug in chronic pancreatitis had proved to be free of complications when applied to humans.

We began to investigate the means of administration in human beings (5). In dogs the anatomic disposition of the excretory pancreatic duct favors experimentation such as ours because of its easy extraduodenal access. In humans, however, the duct must be reached by means of a duodenotomy, which has to be performed upon an organ affected by the inflammatory process.

In order to avoid the transduodenal tract we tried to instill Prolamine in the dead body using balloon probes introduced through choledoctomy, trying to create a chamber in the choledochus terminus. This operation, as well as the retrogressive tract from the tail end of the pancreas, did not ensure the complete refilling of the canicular tree. In humans, only the transduodenum papillar tract could be used to inject the Prolamine. We consider that the frequent ruptures of the duodenorraphies are in part due to the action of the pancreatic secretion. If the drug caused the interruption of the free drainage of the pancreatic fluid from 11 to 15 days, then the risks of the duodenotomy would diminish.

Instillation through the endoscopied tract simultaneous with a laparatomy (essential to investigating the anatomopathologic state of the gland) could be an ideal combination. Yet reflux of Prolamine through the Wirsungian pore could counteract proper ductal refilling. On the other hand, the latest efforts to apply endoscopy in the treatment of chronic pancreatitis have not been altogether satisfactory; furthermore, the catheter might remain imprisoned when the drug solidifies.

Because we were certain of the effects of Prolamine on serious, experimentally induced acute pancreatitis and of its tolerance by human beings, in agreement with European observations we decided in favor of its clinical application. For this purpose we planned a quick check upon each patient presumably suffering from acute pancreatitis, through echography, computerized tomography, and a transparietohepatic cholangiography, and decided upon an early surgical intervention. However, the first application was not in an acute inflammatory case, but rather with the intention of blocking an external pancreatic fistula caused by traumatic rupture of the body of the gland in a patient previously operated on for that reason. The patient was a young man hospitalized at the Hospital Italiano in Buenos Aires. His surgeon, Dr. Beveraggi, had heard about our experimental work and asked us to try Prolamine for the patient.

After catheterizing the fistulous tract and obtaining a pancreatography, we instilled Prolamine. Since the proximal pancreatic duct was not patent, refilling was incomplete, with consequent failure. The fistula reappeared 72 hours later. A few days later we repeated the experiment, without managing to complete the introduction of the catheter. Once again we failed. Dr. Beveraggi reoperated on the patient, effecting a corporocaudal pancreatectomy, thus curing the patient.

Case 1. A 32-year-old woman was urgently operated on for presumptive acute cholecystitis with pancreatic repercussion. After a laparatomy, we found gallstones with no signs of acute inflammation of the gallbladder; a retroperitonium hematoma made exploration necessary. We performed a cholecystostomy, choledochostomy, papillosphincteromy, and Wirsung catheterization, injecting through the latter 7 ml. of Prolamine. The surgical work was ended with a gastrotomy and a jejunotomy.

Postoperatively the patient did well; no complications developed. The serum amylase became normal on the 4th day. The patient started oral feeding on the 15th day and was discharged on the 17th day. Computerized tomography revealed diffused enlargement of the organ and undefined borders. Succeeding tomographies revealed no hypodense images which might have indicated the progression of the illness.

Case 2. A 31-year-old woman was hospitalized after four days of evolving pain, beginning as colic in the right hypochondrium and later becoming continuous. No bile antecedents were reported. During the physical examinations, palpation and sudden decompression of the painful zone caused pain; fever and leukocytosis were revealed. Amylase was reported as normal, which turned out to be erroneous; the immediate postoperative level showed a remarkable elevation. The diagnosis was acute cholecystitis, and she was operated on. On opening the peritoneum the vesicular and retroperitoneal injury were observed. The opening of the gastrocholic omentum revealed a hemorrhagic pancreatitis. The method employed was similar to that described in case 1.

The immediate postoperative period was satisfactory. Later she had a 38°C fever and vomiting. When drainage tubes were removed a pancreatic fistula was observed, initially draining 200 ml per day, a flow which decreased rapidly. The tomographic images showed the evolution of a 6 × 6 cm cystic formation and its subsequent reduction. Later another subhepatic image appeared compatible with an abscess which was spontaneously dissolved when a purulent collection was drained out. This led to the patient's cure.

Case 3. A 27-year-old man was hospitalized ten days after the onset of serious acute pancreatitis. He was urgently operated on. Bloody fluid was found in the peritoneum and fat necrosis as well as gallstones in the gallbladder and common duct. The size and consistency of the pancreas were uniformly increased. This gland presented a diffuse hemorrhagic lesion and no suppuration or secuestrum were observed. Cholecystostomy, choledochostomy, duodenotomy, jejunotomy, and abdominal drainage were effected.

Postoperatively the patient had fever and serious cardiorespiratory problems. On the 9th day, he was reoperated on and the duodenum suture was found to be in normal condition. The body and tail of the pancreas were necrotic and suppurative. A left pancreatectomy was performed. The patient died two hours later.

Discussion

Taking into account the varying evolutions of this illness, we consider early intervention adequate treatment because it allows convenient administration of Prolamine and thus prevents necroseptic injuries and enzymatic toxemia. This course of action has one disadvantage: the surgical treatment is also applied to those patients with minor injuries to the pancreas, which could be easily controlled with medical care. There are no drawbacks whatsoever in following the suggested course of action. Moreover, the postoperative morbidity and mortality of patients who have mild pancreatitis without biliary pathology is very low. Relying on medical treatment would risk losing the chance of administering Prolamine during the initial stage of serious acute pancreatitis. In case 1 the injury was hemorrhagic. We did not find any signs of parenchymal destruction.

In such cases there is a cycle of edema, hemorrhage, and necrosis, in varying order and duration. It is true that not all cases of edematous pancreatitis reach a serious phase and that hemorrhagic-type illness does not necessarily develop into necrosis. A subjective, personal factor rules the development of the illness. This supports the idea of applying the appropriate therapy. Although we cannot draw definite conclusions solely on the evolution of the first two patients treated, we can presume that the procedure is efficient in the treatment of an illness which at present has high mortality rates. The benign nature of the two postoperative periods we observed, in which both patients avoided the habitual enzymatic breakdown, and the excellent clinical evolution of the two patients, confirm this statement. The sole abnormal characteristic of these patients' postoperative periods was tachycardia; its origin has not yet been determined. We would discard the possibility that Prolamine affects the blood vessels. We have started to investigate the possible collateral effects. Unfortunately, the third case arrived at the hospital 10 days after the onset of the illness. We believe that this fact was the main cause of the patient's death. We inferred that the necrosis on the back wall of the pancreas might already have been there in the first operation. If it was, the ineffectiveness of the ductal blockade is explained.

We should point out that in spite of the categorical results achieved experimentally and the excellent evolution of the first two human patients, we cannot assuredly assert that in advanced stages of serious acute pancreatitis Prolamine is a guarantee. Further experiments are required to come to a definite conclusion on the matter. The report of these two observations has been made because this is the first time in medical history that the drug has been employed in the treatment of serious acute pancreatitis in human beings. We believe that diffusion of these observations will help other centers to opt for this course of action and will enable them to gather sufficient research material.

In summary: the intraductal stop has proved to be highly efficient in the treatment of serious acute pancreatitis in dogs. The excellent results obtained in the first two human patients open a promising future in the therapy of this serious illness.

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Azathioprine Experience in Severe, Generalized, Recalcitrant Myasthenia Gravis

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Abstract

Twenty-one thymectomized patients with severe generalized myasthenia gravis resistant to anticholinesterases, steroids,and plasmapheresis were observed on azathioprine over a 5-year period. Only six patients (29%) seemed to improve clinically, and eight patients (38%) demonstrated significant toxicity to the drug. However, the natural fluctuations in clinical course of myasthenia gravis plus gradual improvement observed post-thymectomy can make proper evaluation of additional therapies difficult.

Although there is general agreement on the clinical effectiveness of steroid-induced immunosuppression in myasthenia gravis (MG), the role of azathioprine in similar situations is less clear. Conflicting impressions may be due to the small number of cases reported, the prevailing hesitancy to use the drug in a primary role because of its possible teratogenic and oncogenic effects, and the concomitant use of other treatment modalities (thymectomy, steroids, plasmapheresis). Last, but not least, spontaneous improvement or exacerbation tends to occur in MG, although the clinical course seems to stabilize with time after thymectomy in the majority of patients. Although the European experience with azathioprine in MG has been highly favorable (1–3), this impression was not borne out by a recently published opinion survey on therapeutic preferences from major MG centers around the world (4). Dau reported that neither steroids nor azathioprine alone was capable of providing stable improvement in conjunction with plasmapheresis, but they were able to do so in combination (5). Hawkey et al suggested that there is no synergy between plasmapheresis and azathioprine, but Valbonesi et al reported the exact opposite (6, 7). Witte (8) recently reported favorably on the use of azathioprine in generalized MG, yet was able to show definite improvement solely due to azathioprine in only 33% of cases and encountered a 25% incidence of serious toxicity.

Azathioprine is an antimetabolite which, after hepatic conversion to 6-mercaptopurine, selectively kills dividing cells, inhibits immunoglobulin synthesis and acetylcholine receptor antibody production, and can prevent the induction of experimental autoimmune MG (9–11). There are no convincing data that azathioprine has a selective action on immunoregulatory T-cell subsets (12). The drawbacks are its potential suppressive action on bone marrow, teratogenic effects, increased risk of incurring non-Hodgkin's lymphoma, and toxic effect on the liver (1, 2, 6).

We report on 4 years' experience with azathioprine in a homogenous myasthenic population consisting of 21 patients with severe, generalized myasthenia gravis, all of whom had been thymectomized prevously and who had failed to respond adequately to other forms of immunosuppression.

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Methods

The clinical profile of our patient sample is shown in Table 1. All patients had previously been thymectomized, by either the transcervical or transsternal route. Although many patients had definitely improved on high-dose steroid therapy (up to 100 mg prednisone on alternate days) and chronic intermittent plasmapheresis (2 months to 4 years), their clinical course was unstable and severe disability remained. We also employed azathioprine in that type of patient who, although doing well, could not be weaned from plasmapheresis or high-dose steroids regimens. Eighteen patients were women and three were men. There were seven patients with thymoma and 14 nonthymoma patients, reflecting the higher incidence of thymomas in the more severe forms of MG and in the 40-and-older age group (16 of 21). Duration of MG ranged from 1 to 18 years. All patients continued to take pyridostigmine and prednisone throughout. After proper consent was obtained, patients were started on daily azathioprine (2.5 mg/kg) and continued on this regimen for 6 months. If no clinical improvement was observed by that time, the daily dose was raised to 3 mg/kg. Drug treatment lasted from 8 months to 4 years (Table 2). Azathioprine therapy was continued despite lack of clinical improvement because of prevailing disagreement in the literature as to the time required for this drug to reach maximum clinical effects (1–3, 6, 10). The criteria for improvement were (a) increased muscle strength with decreased functional disability, (b) ability to wean patient from plasmapheresis, and (c) ability to reduce steroid dosage by 50% or more without impairing the patient's functional state and clinical stability.

TABLE 1
Clinical Classification

Pt	Age/sex	Clinical class	Duration of MG	Thymoma	Response to azathioprine
CB	49/F	III	7 yr		+
CF	28/F	III	1¼ yr	Yes	+
GB	57/M	III	2 yr	Yes	–
MC	39/F	IV	18 yr		–
JC	38/F	III	4 yr		–
JC	68/M	III	2 yr		+
ND	54/F	IV	10 yr	Yes	–
HG	58/F	III	1 yr		
CC	40/F	IIB	7 yr		–
LG	50/F	III	3 yr	Yes	
JH	41/F	IV	14 yr		–
PH	58/F	IIB	3 yr		
LL	61/F	III	1 yr	Yes	
KM	30/F	IIB	3 yr		–
CM	45/F	IIB	2 yr	Yes	–
MR	21/F	IIB	3 yr		+
FS	55/F	III	11 yr		–
GW	51/F	III	7 yr		–
EB	40/M	IIB	12 yr		–
ER	65/F	III	4 yr	Yes	+
ER	45/F	III	2 yr		+

TABLE 2
Duration of Treatment

No. of years	No. of patients
Less than 1	3
1	2
1½	3
2	6
3	3
3½	3
4	1

All patients were observed by one or more members of our clinic every 2–4 weeks. Complete blood counts and serum chemistries were performed at those visits. If blood tests remained normal during the first 3 months, the laboratory tests were subsequently repeated at 4- to 6-week intervals only. Serum acetylcholine receptor (AChR) immunoassay determinations were carried out at irregular intervals by the method described elsewhere (13).

Results

Responders. Clinical improvement was observed in 6 of 21 patients (29%) ranging in age from 21 to 68 years and including five women and one man. Two of the six patients had a thymoma. Five of the six patients had elevated serum AChR antibodies. Duration of illness prior to azathioprine therapy ranged from 1 to 7 years, five of the six patients having had MG less than 5 years.

Case 1. A 68-year-old man with a 2-year history of MG, Class III, no thymoma, elevated serum AChR antibody levels, 1 year postthymectomy on 50 to 100 mg prednisone on alternate days plus pyridostigmine, required tracheostomy, nasogastric feedings, and plasmapheresis. Improvement became clinically apparent after about 3 months of azathioprine and continued for 2 years despite reduction of steroids. During the course of azathioprine therapy the patient developed a transient, pruritic macular eruption, which subsided spontaneously.

Case 2. A 21-year-old woman with a 3-year history of MG, Class IIB, without thymoma, with elevated serum AChR antibody titers, had severe bulbar and peripheral weakness despite thymectomy, 50 to 100 mg prednisone on alternate days, and pyridostigmine. Stabilization of clinical MG became apparent after 3 months of azathioprine therapy. Marked clinical improvement persists in the third year of azathioprine treatment despite reduction in steroid dosage. The only observed side effect was transient leukopenia requiring reduction in azathioprine dose.

Case 3. A 28-year-old woman with a 15-month history of MG, Class III, with thymoma and elevated serum AChR antibody titers, had a stormy clinical course with frequent crises despite thymomectomy, thymectomy, pyridostigmine, high alternate-day prednisone (100 mg) therapy, and chronic intermittent plasmapheresis. Azathioprine stabilized and improved the clinical course after about 3–4 months, but had to be stopped after 8 months because of abnormal liver chemistries. The patient's MG exacerbated gradually in the ensuing year. Azathioprine was restarted after liver chemistries had returned to normal. Clinical improvement was again observed within 2 months.

Case 4. A 49-year-old woman with a 7-year history of MG, Class III, without thymoma, but with elevated serum AChR antibody titers, required permanent tracheostomy because of frequent respiratory crises despite pyridostigmine, thymectomy 4 years previously, and high alternate-day prednisone dosage (30–100 mg). Plasmapheresis had been ineffective. Institution of azathioprine therapy was followed by marked clinical improvement 1 year later and was associated with a 70% reduction in steroid dosage. The tracheostomy was closed. The patient is now at the end of the third year of azathioprine therapy without toxic side effects.

Case 5. A 45-year-old woman with a 2-year history of generalized MG, Class III, without thymoma and with elevated serum AChR antibody titers, was started on azathioprine because of unstable, stormy clinical course despite thymomectomy and thymectomy two and a half years previously, pyridostigmine, high-dose alternate-day prednisone (50–100 mg) therapy, and plasmapheresis. Clinical improvement became apparent 3–4 months after onset of azathioprine therapy and has stabilized the patient's clinical course for the past 17 months without toxic side effects.

Case 6. A 65-year-old woman with a 4-year history of severe generalized MG, Class III, with thymoma, had undergone thymectomy 4 months previously. The clinical response to surgery and pyridostigmine was disappointing, and a tracheostomy became necessary. Serum AChR antibody levels were in the low-normal range. The patient responded to alternate-day prednisone (30–50 mg) and plasmapheresis. Plasmapheresis could be discontinued 3 months after the start of azathioprine therapy. Finally, steroids and plasmapheresis were stopped, and after 8 months azathioprine was also discontinued. Two years later the patient remains in complete remission.

In only one of the responders were we able to stop prednisone, plasmapheresis, and azathioprine altogether. In one patient we were able to reduce steroid dosage by 50%–75% but could never eliminate it. Similarly, plasmapheresis intervals could be stretched up to 8 weeks, but not beyond. In two instances when plasmapheresis was stopped, severe clinical symptoms returned within a 1-month period.

Nonresponders. This group comprised 15 patients (71%) ranging in age from 30 to 61 years, two men and 13 women. Five of the fifteen patients had thymoma. Twelve of the fifteen patients had elevated serum AChR antibody levels. Duration of MG prior to onset of azathioprine therapy ranged from 1 to 18 years, five patients having had the illness for 10 years or more.

Acetylcholine Receptor Antibody. Fifteen of twenty-one patients had elevated serum antibody titers. Plasmapheresis and prednisone therapy was followed by marked reductions in serum AChR antibody levels (see Table 3). Addition of azathioprine to the regimen resulted in a smaller, but significant change. In some patients the antibody titer remained in the normal range, whereas in others it fluctuated widely. Table 3 shows average antibody titers in 11 patients in this study before and during a 1-year period of azathioprine therapy. Statistical analysis of AChR antibody ti-

TABLE 3

Acetylcholine Receptor Antibody During Azathioprine Therapy

		Average antibody titer on steroids		
Pt	Baseline antibody titers, µM	Before plasmapheresis, µM (no.)*	Plus plasmapheresis, µM (no.)*	Plus plasmapheresis plus azathioprine, µM (no.)*
GB	15.0	6.2 (3)	4.8 (30)	3.00 (8)
EB	12.4	8.5 (2)	9.4 (17)	10.60 (3)
MC	90.0	72.0 (2)	32.0 (26)	29.00 (10)
JC	1.9	0.7 (3)	0.6 (14)	0.53 (5)
JC	15.8	10.1 (1)	4.8 (11)	3.60 (3)
LL	?	3.2 (1)	0.4 (42)	0.40 (4)
ND	22.7	48.0 (2)	11.0 (42)	6.50 (3)
CG	15.7	38.0 (1)	20.0 (36)	24.00 (4)
MR	4.1	3.5 (2)	3.2 (15)	2.60 (4)
CB	?	31.5 (1)	14.0 (10)	7.20 (3)
CM	31	31.7 (6)	16.6 (33)	17.40 (4)

* No. = number of determinations.

ters before and after azathioprine therapy is as follows:

Baseline versus steroids ($n = 8$)
  Paired differences Minimum = -0.7
    Median = 4.8 Maximum = 8.8
  Wilcoxon two-sample paired signed rank
    test $t^+ = 43, p = 0.006$
Baseline versus steroids and plasmapheresis ($n = 8$)
  Paired differences Minimum = 0.09
    Median = 10.6 Maximum = 58
  Wilcoxon two-sample paired signed rank
    test $t^+ = 45, p = 0.002$
Baseline versus steroids and plasmapheresis and azathioprine ($n = 8$)
  Paired differences Minimum = 1.5
    Median = 12.1 Maximum = 61
  Wilcoxon two-sample paired signed rank
    test $t^+ = 45, p = 0.002$

All paired differences are computed as earlier time point–later time point. To adjust for multiple comparisons of the data, the *p* value must be 0.0083 to be considered significant at the 0.05 level (Bonferrone multiple comparisons).

Toxicity. One patient developed icterus associated with elevated serum alkaline phosphatase, bilirubin, and SGOT and SGPT levels after 5 months of azathioprine use. The patient died of acute liver failure, and postmortem examination revealed acute hepatitis, probably drug related. Two other patients developed transient abnormal increases in serum SGOT and SGPT enzyme levels, which subsided after the drug was stopped.

Four patients developed transient leukopenia to levels of 2000 to 3500 WBC/mm^3, which responded to reduction or cessation of azathioprine.

One patient developed a limited generalized erythematosus macular body rash, which subsided after the azathioprine was stopped and did not recur when the drug was resumed.

No sepsis was observed.

Discussion

Some clinical observations suggest the limited effectiveness of azathioprine therapy in the treatment of MG, but others do not (1–4, 8, 14, 15). To date, no randomized controlled trials have been reported. This is of critical importance in a disease like MG, which has spontaneous clinical fluctuations and for which several forms of medical and surgical therapy are carried out concurrently or within short spans of time. Although there is little doubt about the ability of azathioprine to act as an immunosuppressant, there is no agreement as to the required dosage, the time required before clinical effects can be measured, or the approximate time it takes for the drug to reach maximal effect.

Some observers report onset of clinical improvement as soon as 2 weeks after start of therapy, whereas others mention an average of 4–6 months (1, 2, 3, 16). Still others claim that maximal effects may not be observed for 18 months or more (2, 3, 6). The toxic effects on bone marrow and liver function are well known, but the danger of increased risk of non-Hodgkin's lymphoma is largely based on animal and transplantation studies (15–19). We are not aware of reports of lymphoma after azathioprine in any myasthenic patient.

Experimental animal trials by Abramsky et al suggest that azathioprine suppresses the effector response of cells rather than preventing primary sensitization (11). Others have shown significant declines in OK-T8 (suppressor) cells and changes in the OK T-4-/T8 ratios in MG patients which may be affected by azathioprine (20). The drug has been shown to inhibit immunoglobulin synthesis and to be able to lower AChR antibody titers in MG, although abnormal titers remained in the majority of instances (10, 21). The lack of good correlation between titer and degree of clinical weakness is well known (21–23). Dau feels that neither prednisone nor azathioprine alone or in conjunction with plasmapheresis is able to produce stable, sustained improvement, whereas both drugs used concurrently with plasma exchange were successful (5). In our experience, we were able to attain remission in thymectomized patients with alternate-day steroids plus plasmapheresis (23, 24). Whenever the patients' condition exacerbated on this regimen, increasing prednisone dosage or shortening plasmapheresis intervals, or both, were almost universally successful in reversing a downward clinical course.

In the Swedish-Finnish series of 68 patients, the overall improvement rate was 62%, but all patients had received steroids or undergone thymectomy or both. In only 7% could azathioprine be withdrawn without clinical exacerbation (3). The fact that it took 1½ to 2 years of drug treatment to reach maximal clinical improvement cannot really be ascribed to azathioprine alone. Not only does the clinical course of MG fluctuate spontaneously over a 2-year period, but the time required to reach maximal benefit may have been due to the delayed effects of thymectomy—regardless of azathioprine. Their observation that the older group of patients responded more favorably again holds true for thymectomy alone. Similar comments apply to the Mertens, Hertel, and Matell series (1–3).

Although we cannot be certain that the observed beneficial effects were due to azathioprine alone, it was our clinical impression that the drug stabilized the clinical course and allowed for reduction of other treatment modalities in 6 of 21 patients.

Four of the six responders were more than 35 years old and had suffered from MG for 1–7 years (average 3.2 years). The time elapsed between thymectomy and observed improvement ascribed to azathioprine varied from 1 to 5 years (average 2.6 years). The group included two thymomas. Only one patient responder had a normal serum AChR antibody titer, and it was only this patient who attained a complete remission. Eight of twenty-one patients (38%) had significant toxicity symptoms, with a mortality rate of 1 of 21 (5%). Another recent American series reported a 25% toxicity rate (8). Deaths from azathioprine have also been reported by others (14).

Analysis of our antibody data reveals that azathioprine in combination with steroids and plasmapheresis exerted an additional suppressive effect when compared with baseline values (no treatment), but not when compared with steroids and plasmapheresis as base ($p = 0.12$). However, these values have relatively little meaning in terms of individual prognosis since different patients were on different treatment schedules, e.g., range of steroid dose and duration of treatment, and serum AChR antibodies were not obtained at identical points in time. However, our data confirms the AChR-antibody-lowering effects of steroids with or without plasmapheresis reported previously (5, 6, 22).

Our data do not permit the conclusion that the observed clinical improvement was due to azathioprine during 1–4 years of continuous therapy, despite its additional suppressive effect on serum AChR antibody levels. The onset of clinical improvement after azathioprine therapy varied from 3 weeks to 10 months. If no improvement occurred within the first year of azathioprine treatment, none was observed subsequently. Increasing the dose of steroids with or without increasing the rate of plasmapheresis was able to produce clinical improvement in most instances of clinical exacerbations. This suggests that prednisone was more effective in the short run, but the possibility of a synergistic effect with azathioprine cannot be ruled out.

This study also confirms our previous impression (25) that duration of MG was one of the most influential prognostic factors. Average duration of MG among responders was 3.2 years, versus 6.6 years among nonresponders ($p = 0.002$). Presence or absence of thymoma or elevated serum AChR antibody titers did not correlate with azathioprine treatment response. Controlled randomized studies employing azathioprine prior to thymectomy or steroids over a period of at least 5 years would be needed to prove the effectiveness of azathioprine alone. The practicality, feasibility, and desirability of such a clinical study seem most unlikely. We will continue to use azathioprine as an adjuvant drug in the older population with the aim of stabilizing the clinical course of MG and helping wean patients from high-dose steroids and plasmapheresis dependence.

Summary

Twenty-one patients with severe generalized MG did not do well clinically despite thymectomy, pyridostigmine, plasmapheresis, and high alternate-day prednisone therapy. In six patients the clinical course seemed to stabilize and/or improve after the addition of azathioprine. However, past experience indicates that natural fluctuations in clinical MG plus gradual improvement observed postthymectomy can make proper evaluation of additional therapies most difficult, if not impossible. Eight of twenty-one patients (38%) demonstrated significant toxicity, including one death. Most likely, azathioprine exerts an additional immunosuppressive effect, but this is difficult to evaluate on the basis of available data.

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Inferior Vena Cava Interruption

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Abstract

Interruption of the inferior vena cava was performed in 28 patients for treatment of deep venous thrombosis of pulmonary embolism during the years 1977–1982. The operative indications were failure of anticoagulation to prevent embolism (39%), contraindications to anticoagulation (21%), and complications arising from anticoagulation (11%). Additionally, eight (29%) patients thought to be at risk for deep venous thrombosis or pulmonary embolism underwent inferior vena cava interruption in conjunction with an unrelated surgical procedure. Complete infrarenal ligation of the inferior vena cava was accomplished in 17 patients, the Miles clip was utilized in 7 patients, and the Mobin-Uddin umbrella was placed in 5 patients. There were three postoperative deaths, one with each of the interruption methods. No complications were reported in the surviving patients. A review of inferior vena cava interruption is presented.

Deep venous thrombosis (DVT) and pulmonary embolism (PE) are major causes of morbidity and mortality. The 300 participating hospitals of the Northeastern Region of the Commission on Professional and Hospital Activities reported in 1981 that thrombophlebitis was the admitting diagnosis in 0.15% of all patients and a secondary factor in an additional 0.28% (1). Labeled fibrinogen studies have demonstrated that DVT complicates the course of 27% of post-operative patients (2). Dalen and Albert have estimated that 630,000 cases of symptomatic PE occur each year and result in approximately 200,000 fatalities, thus making PE a common cause of death in the United States (3).

Administration of prophylactic minidose heparin to patients at high risk for DVT and full anticoagulation following the occurrence of DVT or PE have been shown to significantly reduce associated complications (2, 4). Anticoagulation is, however, contraindicated in the immediate postoperative period and in other circumstances where hemorrhage is a likely event or has already occurred. In these instances patients may be managed successfully by inferior vena cava (IVC) interruption. This report summarizes The Mount Sinai Hospital experience with IVC interruption during a recent six-year interval.

Material and Methods

A retrospective study of all patients who underwent interruption of the inferior vena cava at The Mount Sinai Hospital between the years 1977–1982 was conducted. Cases were identified via the International Classification of Diseases Operative Index and individual charts reviewed. Additional data concerning the numbers of hospital discharges, deaths, and primary diagnoses were similarly obtained from the International Classification of Diseases Diagnostic Index.

Results

During the six years 1977–1982, 28 cases of IVC interruption were documented. A total of 225,955 hospital discharges was recorded during the study period (Table). Either deep venous thrombosis (DVT) or pulmonary embolism (PE), or both, were reported in 1,281 patients (0.57%). There were 7,142 deaths, and PE was listed as the primary or secondary cause in 187 (2.6%). Only 2.2% of all patients with DVT and/or PE underwent IVC interruption.

The number of IVC interruptions per year varied from two (1977) to nine (1980) (Table). Age

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TABLE

Hospital Statistics 1977–1982

Year	Hospital discharges	Pts with DVT or PE	Hospital deaths	PE-related deaths No. (%)*	Vena cava interruptions No. (%)†
1977	36,347	300	1,092	37 (3.4%)	2 (0.7%)
1978	36,875	240	1,272	29 (2.3%)	4 (1.7%)
1979	37,875	159	1,138	14 (1.2%)	3 (1.9%)
1980	38,205	173	1,098	21 (1.9%)	9 (5.2%)
1981	38,678	229	1,268	41 (3.2%)	4 (1.7%)
1982	37,975	180	1,274	25 (2.0%)	6 (3.3%)
TOTAL	225,955	1,281	7,142	167 (2.3%)	28 (2.2%)

* Percentages of total hospital deaths.

† Percentages of patients with DVT and/or PE.

at operation ranged from 20 to 78 years, mean 55.3 years. Nineteen (68%) of the patients were women.

Six patients (21%) had contraindications to anticoagulation. Four had neurologic disease or had recently had neurosurgical procedures. One patient had active ulcerative colitis and another patient had an upper gastrointestinal hemorrhage.

Three patients (11%) developed rectal bleeding following anticoagulation. Eleven patients (39%) underwent IVC interruption following failure of anticoagulation to prevent PE.

IVC interruption was performed as a secondary procedure in eight (29%) patients who underwent celiotomy or mediasternotomy for nonembolic disease. Four of these patients had previous episodes of PE and were considered to be at high risk for recurrence following the current operative procedure. The remaining four patients had concomitant DVT.

The interruption procedure most frequently performed (17/28) was ligation of the IVC. The Mobin-Uddin umbrella was inserted in five patients, while seven patients had a Miles clip placed across the IVC. One patient underwent simultaneous IVC ligation and clipping.

Following surgery there were three deaths (11%), one with each of the operative methods. No in-hospital surgical complications were reported in the surviving twenty-five patients. New onset of lower extremity edema was not recorded in any of the patients prior to discharge.

Discussion

Heparin anticoagulation followed by 3–6 months of Coumadin administration is the preferred treatment for DVT or PE. Surgical therapy, first suggested by Homans (5), is generally reserved for those patients in whom medical management is unsuccessful, contraindicated, or associated with complications. Embolic phenomena occur in 2.4% of adequately anticoagulated patients (4), and represent either the new onset of PE or recurrent PE. This group constitutes 4%–43% of patients undergoing IVC interruption (6–9), and in this report represented 39% of patients requiring surgical intervention.

Contraindications to heparin therapy include a previous drug reaction, concurrent bleeding disorders, concomitant hemorrhage, recent neurosurgical procedures, and selected neurologic diseases (6, 7, 9, 10). In our series, 21% of patients underwent IVC interruption for one of the above reasons.

Bleeding complications occur in 1%–20% of fully anticoagulated patients (11, 12). This group represents 13%–45% of patients requiring IVC interruption (6, 7, 9, 10). In this series, 11% of patients experienced hemorrhagic complications following heparinization.

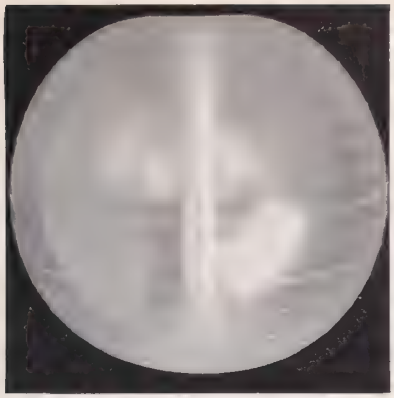
Finally, there is a category of patients who are at risk of developing DVT or PE and undergo IVC ligation during an unrelated operative procedure. This group represented 29% of our patients.

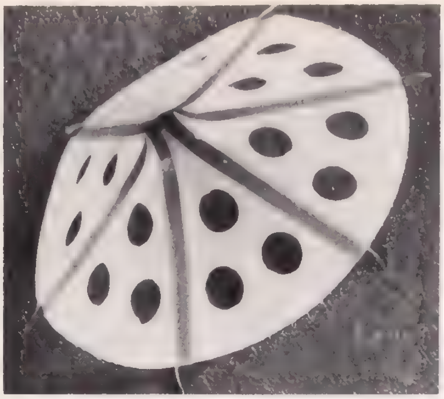
IVC interruption may be accomplished in several ways: complete or partial ligation, extraluminal plication, and intraluminal filtration or obstruction. Complete ligation is usually performed by exposing the IVC via an extraperitoneal approach, encircling the infrarenal IVC with a suture, and totally occluding the lumen. Complete IVC ligation is currently recommended for therapy of septic emboli and recurrent embolization following lesser procedures (13).

IVC ligation is associated with an operative mortality of 5%–40% and late venous sequela of leg edema in 5%–61% of patients (8, 11, 14). Recurrent PE has been reported in 0%–83% of patients (8, 14) and documented to be due to passage of emboli via dilated collateral veins (15). These emboli are rarely fatal.

Partial ligation (16) and plication with sutures (17) or staples (18) were demonstrated to provide merely temporary antiembolic protection (19, 20). These methods enjoyed only a brief popularity. However, the external IVC clip has occupied a central role in the surgical therapy of PE (21–23). Placement of an IVC clip requires exposure of the IVC and is associated with 0%–40% mortality (8, 24). Recurrent PE is reported in 0%–50% of patients (8, 14, 22), while lower extremity venous stasis occurs in 5%–41% (8, 25). Long-term patency of the IVC following placement of the clips is 84%–90% (26, 27).

The Hunter-Sessions Balloon Occluder (Fig. 1) is a unique intraluminal obstructing device (28,





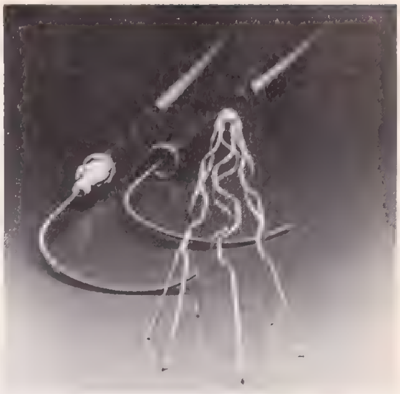


Fig. 1. **Left** Hunter-Sessions Occluder after inflation. Balloon is distended until it becomes wedged in inferior vena cava. (Courtesy of Concept Inc., Clearwater, FL).

Fig. 2. **Center** Mobin-Uddin Umbrella-Filter. Multiple perforations permit blood flow while preventing passage of emboli. (Courtesy of American Edwards Labs, Santa Ana, CA).

Fig. 3. **Right** Greenfield Vena Cava Filter and its introducer. Space between wires in a fully opened filter is 2 mm at apex and 11 mm at base. (Courtesy of MEDI-TECH, Inc., Watertown, MA).

29) that is introduced under local anesthesia via the internal jugular vein. Following confirmation of its position distal to the origin of the renal veins, the balloon is inflated to a pressure sufficient to prevent migration. The balloon deflates over the next 6–18 months, leaving an intracaval fibrotic mass that occludes the IVC (29). This instrument has the advantage of (a) not containing any sharp anchors that might perforate the IVC, (b) possessing intrinsic venography capability allowing precise placement, and (c) not possessing a surface proximal to the site of interruption on which a clot could develop.

Hunter has reported late follow-up of 100 patients (29, 30). There have been no instances of balloon migration and only one episode of recurrent PE. Of these patients, 29% suffered lower extremity edema; only two of the patients in this group were disabled. There were 16 hospital deaths among these patients, none of which was attributable to balloon insertion.

Mobin-Uddin introduced an intraluminal filtration device in 1969 (31, 32). The model currently approved for use is a 28-mm diameter, umbrella-shaped object with multiple 3-mm perforations to permit blood flow, and six stainless steel spokes radiating from a central hub to provide anchorage (Fig. 2). The folded umbrella is inserted under local anesthesia via the internal jugular vein, advanced to an infrarenal position where it is opened, and its six spokes lodged in the IVC wall.

The morbidity associated with insertion has been reported as 6%–8% (6, 33, 34) and usually consists of wound hematoma or minor misplacement. Retroperitoneal hematoma secondary to perforation of the IVC may occur. No deaths have been ascribed to placement of this instrument, though hospital mortality associated with the underlying disease has ranged from 4%–10% (6, 9, 33).

The major drawback of this device has been the poor long-term patency rate of 27%–60% (30, 33). Venous stasis and leg edema occur in approximately 20% of patients following umbrella insertion, presumably as a result of thrombosis of the IVC (6, 33). Additionally, a number of instances of clot formation above the device have been documented (8).

PE following umbrella insertion has been reported in 3%–12% of patients (9, 33), though Mobin-Uddin claims a lower incidence of 0.5% (30). Whether these PE occur via collaterals that formed as a result of IVC thrombosis or from a thrombus on the proximal surface of the umbrella has not been determined. Therefore, in an effort to decrease the incidence of IVC thrombosis and PE, the umbrella filters are now heparin-coated. Results await further clinical experience.

In 1973, Greenfield presented his laboratory experience with a cone-shaped wire filter that appeared to fulfill the requirement of preventing PE while maintaining IVC patency (35). The device consists of six strands of No. 306 stainless steel wire that radiate at angles of 35° from a central focus (Fig. 3).

The Greenfield filter may be inserted under local anesthesia via either the internal jugular vein or the femoral vein, the only intraluminal device to provide this option (36). Following confirmation of an infrarenal position, the filter is released from its carrier and held in place by the hooked ends of the wires impacting the wall of the IVC. Morbidity associated with insertion is similar in nature and frequency to that of the umbrella and is in the range of 7%–12% (7, 33). No deaths have been attributed to the operative procedure.

The patency rate of the Greenfield filter has consistently been reported as greater than 95% (7, 33, 36). Emboli trapped in the filter are lysed by the plasminogen system. As a consequence of continued IVC blood flow, the incidence of venous stasis and lower extremity edema is the lowest of all interruption methods and has ranged from 0%–10%, the majority of cases classified as minor (7, 33). PE following filter placement has been reported in 2%–3% of patients (33, 37), and significant migration of the filter is a rare event (3, 7, 33). Since 1983, the Greenfield filter has been the most frequently employed method of IVC interruption at this institution.

At the present time, all methods of IVC interruption require a surgical procedure. However, recent reports have demonstrated the feasibility of percutaneously inserted wires that assume a coil form when exposed to body temperature (38, 39). Difficulty in permanently anchoring these devices has impeded clinical application.

In summary, the surgical treatment of PE has advanced considerably in the half-century since Homans first suggested ligating the femoral vein. Procedures involving exposure of the IVC with ligation or plication are associated with a high operative mortality and an increased incidence of lower extremity venous stasis and edema. The Greenfield filter is currently the interruption method of choice because of its ease and options of insertion, high patency rate, and effectiveness in preventing PE.

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Idiopathic Pulmonary Hemosiderosis: The Importance of a Chest Radiograph in Children with Unexplained Anemia

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Abstract

Four patients with idiopathic pulmonary hemosiderosis were studied. In each case the disease first presented without pulmonary symptoms. A chest radiograph was not performed in three affected children whose chief initial finding was unexplained anemia; this resulted in diagnostic delays ranging from 4 to 14 months. In contrast, idiopathic pulmonary hemosiderosis was promptly diagnosed in a fourth patient whose abnormal routine chest radiograph focused attention on the respiratory system. A chest radiograph is recommended for children in the initial workup of unexplained iron-deficiency anemia to rule out pulmonary hemorrhage as its etiology.

Idiopathic pulmonary hemosiderosis is an uncommon disease of unknown etiology characterized by recurrent intrapulmonary hemorrhage. The diagnosis is strongly suggested in a child or young adult by the triad of iron-deficiency anemia, hemoptysis, and widespread alveolar infiltrates on chest radiographs, which clear rapidly and reveal an underlying interstitial disease process. However, it is not generally appreciated that hemoptysis and other pulmonary symptoms are usually absent at initial presentation, and the correct diagnosis is often delayed because a chest radiograph is not performed during the evaluation of unexplained anemia. The current trend to eliminate seemingly unnecessary routine-admission pediatric chest radiographs has resulted in delaying the diagnosis of idiopathic pulmonary hemosiderosis in children with unexplained anemia. Four new cases of idiopathic pulmonary hemosiderosis are reported, emphasizing techniques and problems relevant to expediting the radiologic-clinical diagnosis of this enigmatic disease.

Case Reports

Case 1. A 6-year-old white girl was evaluated for sudden onset of tachypnea, pallor, weakness, fever, and hematemesis. The child's medical history was significant for two prior admissions during the previous 12 months for severe, recurrent, hypochromic and microcytic anemia, the etiology of which had never been satisfactorily explained despite an extensive workup of the gastrointestinal tract for evidence of blood loss. A barium enema, upper gastrointestinal series, small-bowel series, and technetium pertechnetate "Meckel's" scan had been previously performed and were normal. No chest radiographs were performed during the first two hospital admissions or during the patient's follow-up visits as an outpatient.

No respiratory symptoms appeared until the time of the third hospitalization, a full year after medical documentation of the patient's severe anemia. At that time, the child was in acute respiratory distress with a respiratory rate of 80/min; she was febrile to 101°F and had a 160/min apical pulse. There was a single episode of vomiting up small flecks of blood but no hemoptysis. A chest radiograph was then performed (Fig. 1), which revealed patchy alveolar infiltrates. A radiograph performed 72 hr later (Fig. 1) showed

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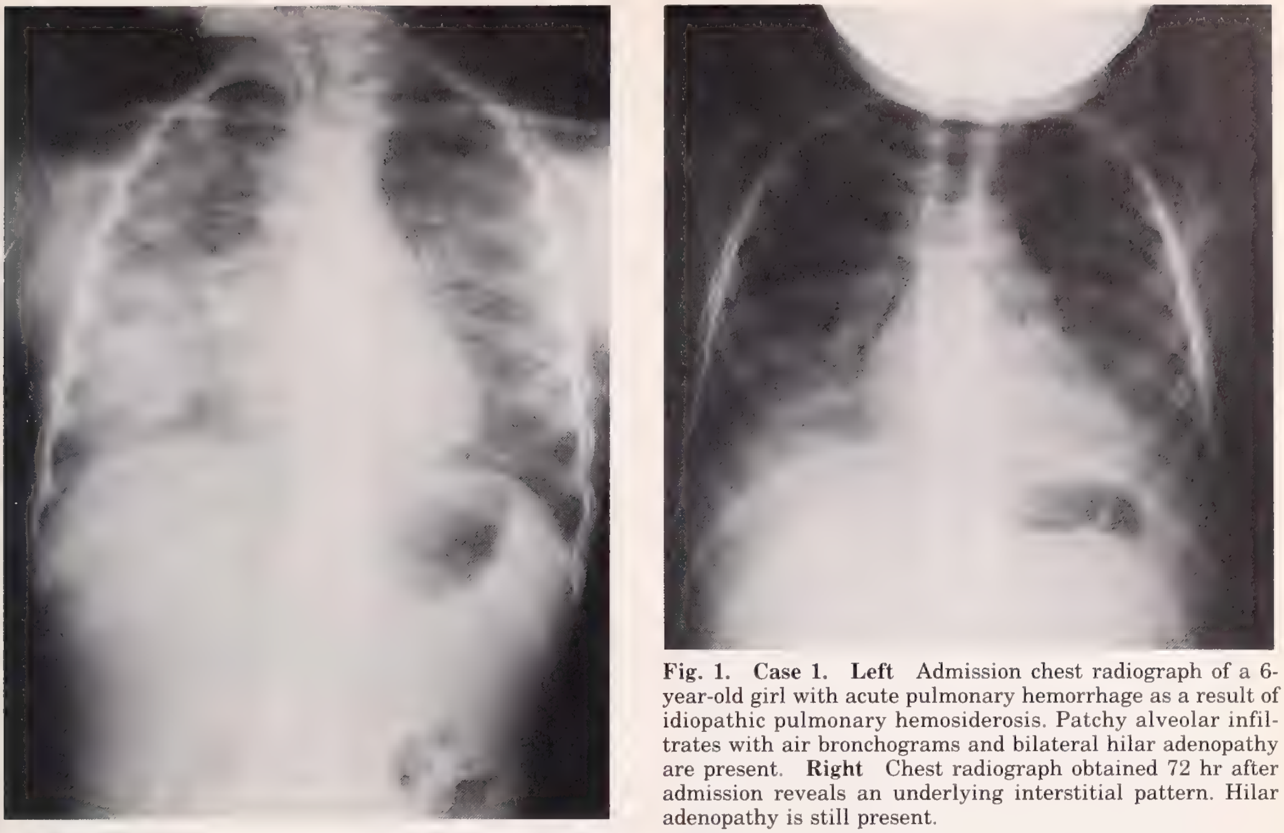


Fig. 1. Case 1. Left Admission chest radiograph of a 6-year-old girl with acute pulmonary hemorrhage as a result of idiopathic pulmonary hemosiderosis. Patchy alveolar infiltrates with air bronchograms and bilateral hilar adenopathy are present. **Right** Chest radiograph obtained 72 hr after admission reveals an underlying interstitial pattern. Hilar adenopathy is still present.

virtual resolution of the alveolar densities and evolution to a predominantly reticulonodular interstitial pattern. Pathologic findings after an open-lung biopsy confirmed the radiologic-clinical diagnosis of idiopathic pulmonary hemosiderosis. Follow-up films showed persistence of the interstitial pattern.

Case 2. A 5-year-old black girl was started on iron therapy after being noted to be anemic. She was admitted for evaluation, but no chest radiograph was performed. Four months later she started coughing and sneezing and was brought to a hospital emergency department after her sputum became blood-tinged. Her hemoglobin was found to be 4.0 gm/dl. A chest radiograph (Fig. 2) was then obtained; it showed bilateral fluffy, perihilar, and basilar infiltrates. Gastric washings and sputum were positive for hemosiderin.

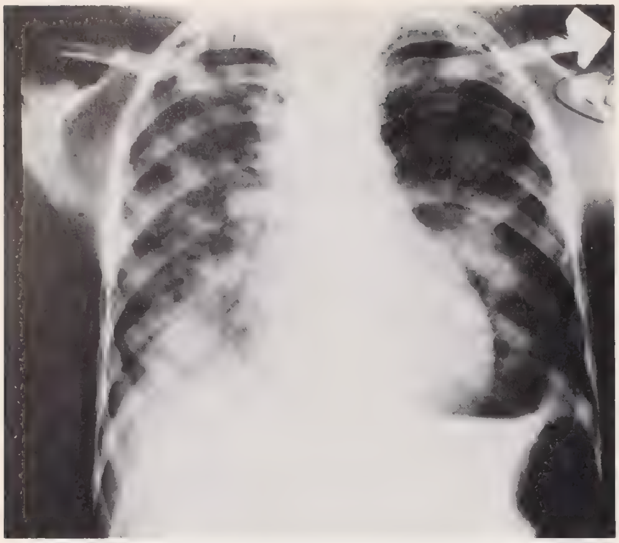
A follow-up film obtained 10 days later showed increased interstitial markings (Fig. 2). A lung biopsy confirmed the presence of idiopathic pulmonary hemosiderosis. Follow-up films (including a chest CT scan) obtained over the next 8 years demonstrated repeated alveolar infiltrations, which cleared rapidly to reveal an increasingly more pronounced interstitial pattern.

Case 3. A 10-year-old white boy was seen by his private family physician for pallor and weakness. The child was otherwise asymptomatic. He was discovered to be anemic and treated on an outpatient basis with iron therapy for 14 months. He then experienced severe shortness of breath without hemoptysis. A chest radiograph was first performed at that time; it showed a mixed alveolar and interstitial lung pattern. The alveolar infiltrates cleared rapidly, and a tentative diagnosis of idiopathic pulmonary hemosiderosis was made. This was confirmed by a subsequent biopsy.

Case 4. A chest radiograph (Fig. 3) performed on an asymptomatic black boy during a routine physical examination revealed markedly increased interstitial markings. A medical workup was then immediately started. Computed tomography (Fig. 3) demonstrated diffuse interstitial fibrosis, alveolar infiltrates, hilar adenopathy, and pleural thickening. The latter findings were not discernible on the conventional chest radiograph. Lung biopsy demonstrated idiopathic pulmonary hemosiderosis, although the patient remained asymptomatic for nearly 2 years.

Discussion

The cause of pulmonary hemorrhage in idiopathic pulmonary hemosiderosis is unknown. The onset of symptoms usually occurs prior to age 10.



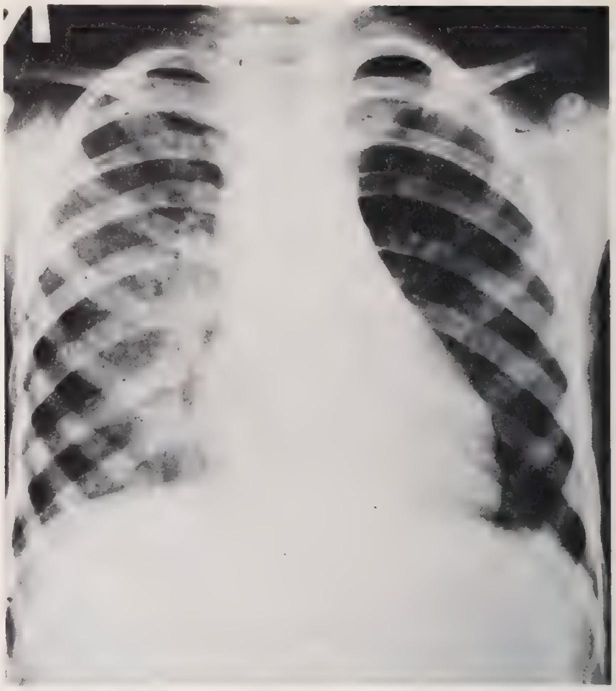


Fig. 2. Case 2. Left Admission chest radiograph of a 5-year-old girl with idiopathic pulmonary hemosiderosis showing patchy alveolar infiltrates similar to those in Fig. 1. **Right** Ten days later, increased interstitial markings are visualized with clearing of alveolar infiltrates.

The sex distribution is approximately equal in younger patients; there is a two-to-one male predominance after the first decade of life (1). Goodpasture's syndrome has identical thoracic manifestations as idiopathic pulmonary hemosiderosis, but there is associated renal disease, and it predominantly affects males over the age of 16 (2). Some researchers (3) have categorized all forms of pulmonary hemosiderosis into a clinicopathologic syndrome complex linked together by pulmonary hemorrhage and similar radiographic findings.

Pathologic findings are those of massive intraalveolar hemorrhage with hemosiderin-laden macrophages present in the alveoli, bronchioles, and pulmonary interstitial tissues (4) (Fig. 4). Inflammation and vasculitis are not present, although diffuse interstitial fibrosis is evident in chronic cases. Specific iron stains show dramatic evidence of iron deposits and iron-laden macro-

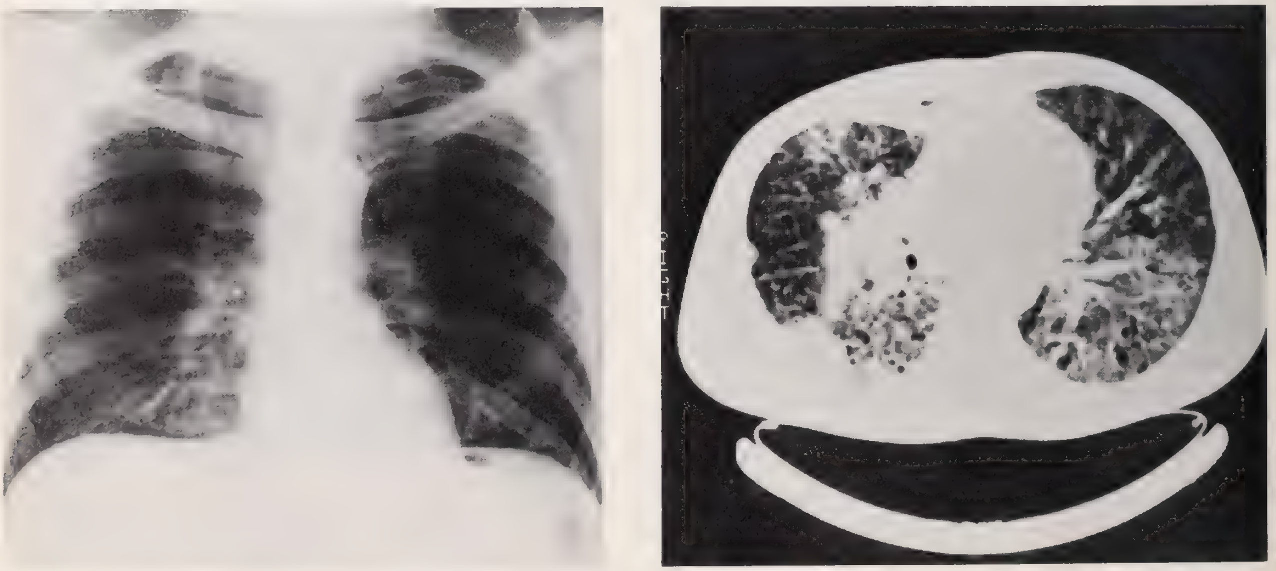


Fig. 3. Case 4. Left Routine chest radiograph of asymptomatic black boy. Increased interstitial markings were later determined to be a result of chronic pulmonary hemorrhage. **Right** Computed tomographic slice of chest of same individual reveals diffuse interstitial fibrosis. Alveolar infiltrates, hilar adenopathy, and pleural thickening, which are not apparent on the plain chest radiograph, are present.

phages (Fig. 4). The absence of antiglomerular basement membrane antibody on immunofluorescent staining must be demonstrated to distinguish idiopathic pulmonary hemosiderosis from Goodpasture's syndrome (2). Electron microscopic findings may also have a future role in distinguishing the histologic features of these two entities (5).

The dynamic radiographic findings in idiopathic pulmonary hemosiderosis occur in synchrony with the pathologic changes. Acute pulmonary hemorrhage is reflected radiographically by multiple patchy densities, particularly in the perihilar and lower lung fields, which represent "air-space" consolidation by blood. Air bronchograms and hilar adenopathy are usually present (6). The alveolar infiltrates then clear rapidly and predictably in a few days as the blood is transported by macrophages into the pulmonary interstitial tissues. A persistent reticulonodular pattern is evident in asymptomatic patients with inactive disease (case 4), and it also appears upon clearing of the superimposed acute alveolar infiltrates from fresh episodes of recurrent pulmonary hemorrhage (cases 1–3) (7).

The differential diagnosis for this type of alveolar filling process includes pulmonary alveolar proteinosis, pulmonary edema, collagen vascular disease, *Pneumocystis carinii* pneumonia, and unusual manifestations of other types of pneumonia (8). However, the patient's age, a history of unexplained iron-deficiency anemia, and the rapid clearing sequence revealing an underlying interstitial pattern of lung disease should eliminate most diagnostic alternatives. Although individual chest radiographs are nonspecific, the changing radiographic pattern is very suggestive of pulmonary hemorrhage when clinical information is available.

Although hemoptysis is a common manifestation of advanced idiopathic pulmonary hemosiderosis, it is not always appreciated that this symptom is frequently absent initially. Three of the four patients presented in this study had no pulmonary symptoms at all for at least 1 year after first coming to medical attention. In a study of 26 patients with idiopathic pulmonary hemosiderosis (9), Matsaniotis and associates reported that only one patient presented with overt hemoptysis and just four others had a history of blood-tinged sputum. Thus, more than 80% of patients had no history of hemoptysis upon initial presentation. Dyspnea was absent altogether in more than 60% of the patients studied. The literature (7,10–17) reports numerous cases of idiopathic pulmonary hemosiderosis presenting solely with iron-deficiency anemia. However, these cases were often reported because the absence of hemoptysis was thought to be an unusual clinical presentation. Even when there is a history of minor episodes of dyspnea or hemoptysis, it may be attributed to chronic bronchitis (8) and be deemed irrelevant in the workup of anemia. The clinician and radiologist must therefore be cognizant of possible pulmonary pathology in every patient with unexplained iron-deficiency anemia, regardless of pulmonary symptomatology.

The risks and costs of radiography in children are controversial issues (18,19). The performance of chest radiographs solely because of hospital admission has been previously reported as medically and economically unjustifiable (20). However, a chest radiograph performed on patients with unexplained anemia will expedite the diag-

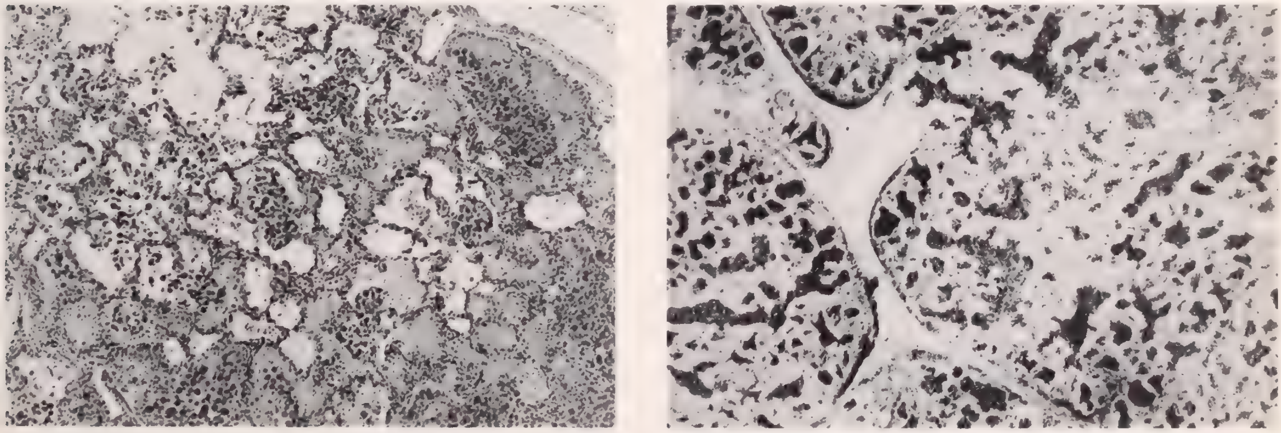


Fig. 4. Case 1. Left Photomicrograph of lung tissue from a child with idiopathic pulmonary hemosiderosis revealing acute and chronic hemorrhage into alveoli (H&E, original magnification ×63). **Right** Photomicrograph of lung tissue with iron-binding stain demonstrating massive amounts of intraalveolar iron in patient with idiopathic pulmonary hemosiderosis (Prussian blue stain, original magnification ×25).

nosis of idiopathic pulmonary hemosiderosis. As was seen in the first case presented, a series of high-radiation-dose radiologic examinations may otherwise be performed to determine the source of blood loss. The need for these expensive and potentially harmful tests might be obviated by a preliminary chest radiograph.

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Cytomegalovirus Infection and Hemolytic Anemia due to Glucose-6-Phosphate Dehydrogenase Deficiency

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Abstract

A patient with red-cell glucose-6-phosphate dehydrogenase deficiency developed hemolytic anemia secondary to cytomegalovirus mononucleosis. This is the first reported instance of this association.

Cytomegalovirus infection has been recognized as a distinct clinical syndrome since isolation of the virus in 1956 (1–3), although viral inclusions typical for cytomegalovirus had been described in 1932 (4). Many of the initial viral isolations were from postcardiac-bypass patients who had received blood transfusions during surgery and had developed the so-called postperfusion syndrome (5). Subsequently, the virus was found with some frequency in renal transplant recipients (6), as a fatal infection in neonates (7), and also in patients with neoplastic diseases (8, 9). In 1965, the first description of cytomegalovirus (CMV) infection leading to a mononucleosis-like syndrome appeared (10). This febrile illness differs from typical infectious mononucleosis in that posterior cervical lymphadenopathy and pharyngitis are usually absent. Atypical lymphocytosis, mild liver function abnormalities, and splenomegaly are seen, with a febrile course lasting three to six weeks (11).

Hemolytic anemia has been reported in association with CMV infection (12–14). These have generally been antiglobulin-positive, warm autoantibodies, with IgG elutable from the red-cell membranes. Cold agglutinins have been implicated less commonly (15). Similar to Epstein-Barr virus mononucleosis, the cold agglutinin can be an IgM antibody with anti-i specificity.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is ubiquitous; over 150 variants have been recorded to date (16). It is X-linked and therefore manifest for the most part in males. Hemolysis may occur following exposure to certain drugs such as the antimalarials or sulfonamides. Similarly, certain infections may trigger a hemolytic episode. Hemolysis has been associated particularly with viral hepatitis (17–19). To our knowledge, this is the first reported instance of acute hemolysis from G6PD deficiency in association with CMV mononucleosis.

Case Report

This 42-year-old black man was hospitalized with a one-week history of fever of 38.3° to 38.9°C (101° to 102°F) with sore throat, night sweats, and increasing nausea and vomiting. He had complained of headache for a few weeks, for which he had received propranolol.

The medical history was significant for gastric ulcer and spontaneous pulmonary embolus four years earlier. A possible episode of hepatitis with dark urine had occurred fifteen years previously.

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There was a known history of situs inversus. The patient was heterosexual. The family history was negative for hematologic disease.

The physical examination revealed an acutely ill black man. The blood pressure was 110/70 mm of mercury, pulse 110 per minute, temperature 38.3°C (101°F). There were no palatal lesions, significant pharyngitis, or icterus. There was no significant lymphadenopathy. The lungs were clear and cardiac examination findings were all normal except for tachycardia. No enlargement of the liver or spleen was present. There was no edema, nor were there any neurologic abnormalities.

Four days prior to hospitalization, the following laboratory studies were obtained: hemoglobin 10.6 gm per dl; hematocrit 33 volumes percent; and white blood cell count 5,400 per mm^3, with 37% polymorphs, 47% lymphocytes, 2% atypical lymphocytes. Reticulocytes were 6.5%, platelets 401,000 per mm^3, SGOT 363 units, SGPT 178 units, alkaline phosphatase 248 units (normal level 30-105 units), LDH 2475 units, total protein 7.3 gm per dl, albumin 4.0 gm per dl, bilirubin 1.8 mg per dl, indirect bilirubin 1.6 mg per dl.

On the second hospital day the following studies were obtained: hemoglobin 9.8 gm per dl, hematocrit 29.5 volumes percent, prothrombin time 14 seconds (control 12 seconds), partial thromboplastin time 22 seconds, plasma hemoglobin 3.0 mg per dl, haptoglobin 59 mg per dl (normal level 100–300 mg per dl). Hemoglobin electrophoresis was AA, SGOT 409 units, SGPT 22 units, glucose 91 mg per dl. A bone marrow examination revealed erythroid hyperplasia and normal iron stores. Further study findings included cold agglutinin titer of 1:4, toxoplasma IgM titer less than 1:16, and negative findings on antiglobulin test, heterophil and mononucleosis slide test, hepatitis-B surface antigen, Donath-Landsteiner test, sucrose hemolysis test, antinuclear antibody, and blood cultures. A CMV IgG complement-fixing titer was 1:1024. A CMV IgM antibody titer was not obtained. A G6PD assay was 0.51 units (normal level 5–10) at a reference laboratory. On the seventh hospital day the LDH was 211 units (normal level 150–250 units), and bilirubin 0.3 mg per dl.

The liver/spleen scan, chest x-ray, and upper gastrointestinal series were normal.

Additional studies performed two weeks later by Dr. K. R. Tanaka at Harbor-UCLA Medical Center revealed the following: hemoglobin 12.9 gm per dl, hematocrit 37.5 volumes percent, white blood count 6,790 per mm^3, red blood cell count 3.75 million per mm^3, reticulocytes 2.9%. Further assays revealed a decreased value of 0.52 units (normal level 2.97–3.83, mean 3.47 units) for red blood cell G6PD activity, normal 6-phosphogluconic dehydrogenase activity and decreased red blood cell glutathione content. Red-cell hexokinase activity was increased consistent with recent hemolysis and regeneration of new cells. A Heinz-body test was strongly positive, 89% of the red cells demonstrating Heinz bodies.

Discussion

Our patient appears to represent the first reported case of acute hemolytic anemia from G6PD deficiency associated with CMV infection. Other etiologies for his fever and anemia were sought, but not identified. The clinical course and laboratory studies support this conclusion.

CMV infections can be acquired congenitally by maternal-fetal transfer, by intimate exposure to infected hosts, or by transfusion with infected blood products (1–3). The course can be fatal in the neonate, but in the adult is usually a self-limited infection lasting three to six weeks. There is no established treatment except for symptomatic and supportive measures. The mononucleosis syndrome is seen in young adults, causing fever and malaise, liver function abnormalities, and, less commonly, hepatosplenomegaly (1). Sore throat and lymphadenopathy are less often seen than in typical Epstein-Barr virus mononucleosis. Blood smears reveal atypical lymphocytes. CMV mononucleosis only accounts for 8% of all cases of mononucleosis-like illnesses. The CMV IgM antibody titer is elevated early in the course of infection and serves as a specific diagnostic test. The complement-fixing antibody rises through the course of infection (20). We believe our patient demonstrated the necessary clinical and laboratory criteria for the diagnosis of CMV mononucleosis.

Hematologic complications of CMV infection have included immunohemolytic anemia (1) and autoimmune thrombocytopenia (21, 22). Hemolytic anemia has generally been antiglobulin positive, with IgG elutable from the red-cell membrane (12–14). A rare patient has had cold agglutinin induced hemolysis with anti-i specificity (15). In addition, other immunologic abnormalities have been detected in patients with CMV infection (23). These have included antinuclear antibodies, cryoglobulins, and rheumatoid factor. Recently, defective T-lymphocyte function has been reported in fatal CMV infections in bone marrow transplant recipients (24). No autoimmune phenomena were detected in our patient, although specific lymphocyte function studies were not performed.

G6PD catalyzes the initial step in the pentose phosphate pathway, thereby converting nicotinamide adenine dinucleotide phosphate to nicotinamide adenine dinucleotide phosphate reduced form (NADPH). NADPH serves as a cofactor for glutathione reductase, which maintains glutathione in the reduced form. Reduced glutathione preserves sulfhydryl groups within the red cell. It is also a cofactor in the reduction of hydrogen peroxide to water and oxygen. If reduced glutathione is decreased due to G6PD deficiency, then hemoglobin is denatured by increased levels of hydrogen peroxide. The denatured globin forms insoluble masses (Heinz bodies) which distort the red-cell membrane. During splenic passage, these distorted cells are removed by the reticuloendothelial components in the splenic pulp (16).

The most common types of G6PD deficiency in the world are the A minus (black type) and the Mediterranean type (16). The A minus type does not cause a chronic hemolytic anemia, but hemolysis may be induced by oxidant stresses such as drugs or infection. Many drugs have been associated with inducing or exacerbating hemolysis in G6PD-deficient individuals. The principal drugs are the antimalarials, sulfonamides, and the furantoins (16). Infections, including bacterial and viral, have been associated with hemolytic episodes (25). This has been especially so with viral hepatitis (17–19). The mechanism of hemolysis from infection is thought to be related to increased hydrogen peroxide generation, which overwhelms the available enzyme in G6PD-deficient patients. It is of interest that our patient developed acute hemolytic anemia due to the underlying CMV infection. The episode was self-limited, with a fairly prompt return to a near-normal hemoglobin in two weeks. It is presumed that our patient had the A-minus type of G6PD deficiency.

In our patient with CMV infection, documented acute hemolytic anemia due to G6PD deficiency occurred. The patient did have mild hepatic inflammation with the infection which, perhaps, may link this episode with those associated with viral hepatitis. Since G6PD deficiency is relatively common, we believe this association is more frequent than realized. It is conceivable that our patient's episode of hepatitis fifteen years earlier was in part a hemolytic event.

It is our recommendation that any patient with CMV infection, or for that matter any infection, with associated hemolytic anemia should be assessed for G6PD deficiency.

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Venous Air Embolism: Case Report and Review

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Venous air embolism is a fairly uncommon, although potentially fatal event. Its incidence is difficult to determine because the entrainment of air into the venous circulation can occur in a wide variety of circumstances. In the great majority of these clinical situations early recognition and treatment can prevent tragic sequelae to what is frequently iatrogenic disease. The intensivist should be aware of the presentation, pathophysiology, and treatment of this disease entity. A report on a patient in whom air embolization occurred is presented.

Case Report

A 45-year-old white male physician with no significant medical history sought medical attention for difficulty in hearing. Subsequent work-up documented a 4-decibel hearing loss in the high-frequency range on the left side, and computerized tomography revealed a 3.7 cm left acoustic neuroma. The patient was scheduled for surgical removal of the tumor. Preoperative physical examination and laboratory values were otherwise within normal limits (chest radiograph, Fig. 1). Prior to surgery the patient was begun on propranolol 40 mg every 6 hours and Decadron 4 mg every 6 hours, the protocol for our neurosurgery patients.

Balanced general anesthesia was administered using Thiopental, droperidol, fentanyl, pancuronium, nitrous oxide, and oxygen, and the patient was maintained on controlled ventilation. The patient received 80 gm of urea at the time of induction.

A radial arterial line was inserted, and a central venous catheter inserted from the right antecubital vein was positioned at the junction of the superior vena cava and right atrium and position was confirmed by doppler (Medasonics, Mountain View, Ca.) and chest radiograph. The doppler probe was positioned over the right atrium, and military antishock trousers (MAST) inflated at 20 mm Hg. The central venous pressure was 7 mm Hg. The patient was placed in the sitting position (45° angle) with his knees at heart level. A 12 mm Hg gradient between the right side of the heart and the superior margin of the incision was measured.

Surgery was performed through a posterior craniotomy. With the dura opened, doppler monitoring of the right atrium detected a change in flow pattern consistent with air entry. Small amounts of air were aspirated from the central venous catheter (less than 50 cc). End tidal $PaCO_2$ monitoring (Hewlett-Packard Corp., Waltham, Mass.) demonstrated a marked decrease in end tidal CO_2 (from 28 to 14 mm Hg) while simultaneous arterial $PaCO_2$ showed progressive $PaCO_2$ retention. The patient became hypotensive (70 mm Hg systolic) and surgery was terminated due to persistent air embolism.

Intraoperatively, the estimated loss of blood was 500cc, urine output 1200cc, with 2,000cc of fluids administered intravenously. Routine laboratory values were normal, and a serum osmolarity of 315 mOsm and a urine osmolarity of 670 mOsm were obtained. A chest radiograph performed in the immediate postoperative period is seen in Fig. 2. He was immediately transferred to the intensive-care unit after reversal of neuromuscular blockade and extubation.

Upon arrival at the unit the patient's blood pressure was 80/40 mm Hg and his heart rate 70/minute. Initial arterial blood gases on an FIO2 of

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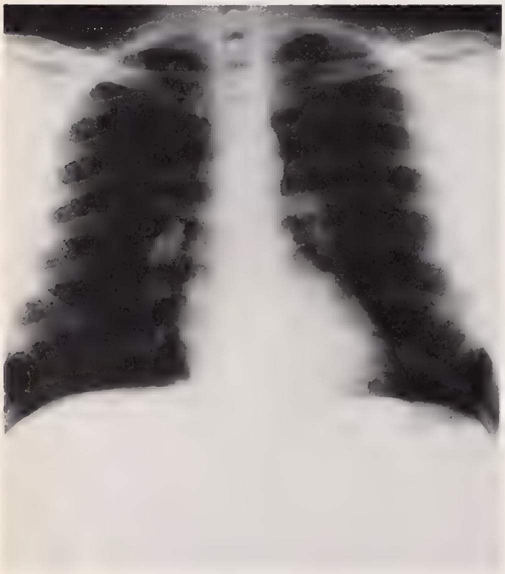
35% were PaO2 62 torr, PaCO2 31.4 torr, pH 7.39. Physical examination was significant for tachypnea with normal breath sounds. No cyanosis was noted. Management in the intensive-care unit consisted of supportive care. His blood pressure responded to fluid administration (128 mmHg systolic) and he remained hemodynamically stable. Arterial blood gases returned to normal with resolution of the alveolar–arterial gradient within 12 hours. His chest radiograph cleared during the next 24 hours and no clinical evidence of arterial air embolism was noted. Serum osmolarity was 310 mOsm initially, 303 mOsm on postoperative day one, and returned to normal on day 2. Ten days later the patient was reoperated on; removal of the residual tumor was accomplished without recurrence of air embolism.

Discussion

Posterior fossa craniotomy performed with the patient in the sitting position is one of the operative procedures known to have an increased incidence of air embolism; reports vary between 21% and 39% (1–4). Although the sitting position offers a neurosurgeon better access and hemostasis, it creates a pressure gradient that develops between the venous circulation and the right side of the heart. When the head is elevated, cranial venous pressure is less than central pressures facilitating air entry (5). This gradient is further augmented by negative pressures generated by spontaneous inspiratory efforts.

The constellation of hypotension, arterial hypoxemia, and an increase in physiologic dead space—manifested by decreasing end tidal pCO_2—indicate pulmonary embolism. Precordial doppler monitoring frequently records changes in tone which signal venous air embolization. Previous investigators have demonstrated a high sensitivity in detecting clinically significant air entry using this method (1, 4). Elevation of central venous pressures is common, and aspiration of air from a central venous catheter provides the entrance of air into the venous system. This procedure is said to mitigate the degree of embolization. Other clinical findings frequently include dyspnea, tachypnea, tachycardia, cough, chest pain, and wheezing. A "mill-wheel murmur" has been described as further substantiation of air embolism (6). EKG monitoring can show ischemia, arrhythmia, bradycardia, and acute cor pulmonale.

Reports vary as to how much air may cause vascular collapse. Gottlieb et al (6) acknowledge that no lethal dose has been determined in humans, but that a volume greater than 300 ml may produce death. Animal studies have shown that the rate of ingress of air as well as the volume of gas administered can contribute to cardiovascular compromise. Verstappen et al (7), working with dogs in the steady state, showed that gas



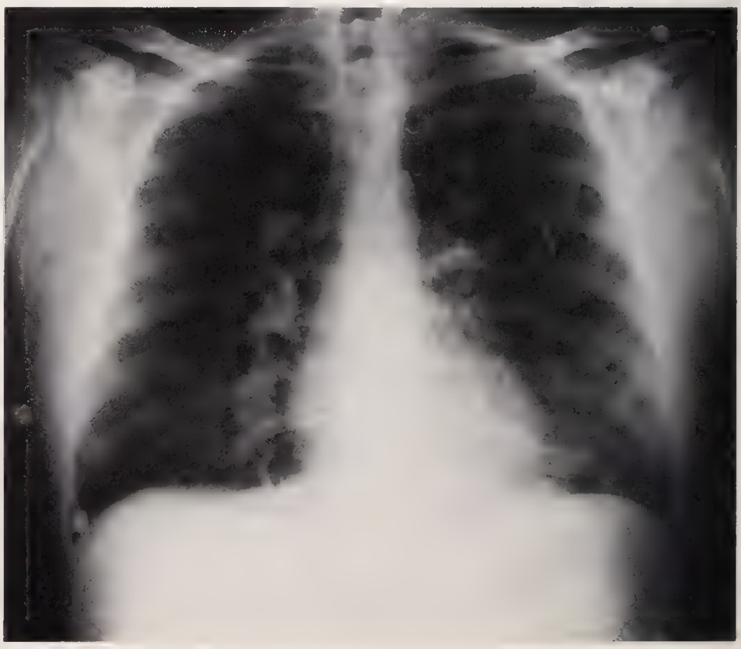


Fig. 1. Left Preoperative chest radiograph.

Fig. 2. Right Chest radiograph demonstrating the interstitial pulmonary edema.

infusion caused a slow rise in the pulmonary artery pressure (PAP) which rose to a maximum within 10–15 minutes. The degree of pulmonary artery hypertension correlated with the rate of infusion of the gas. In contrast, gas injection caused a more rapid rise of PAP (30–60 sec), and the extent of rise was positively correlated with the volume of injected gas. In their study the PAP reflected the degree of embolization when the RV was able to maintain its output. PAP fell when the RV began to fail and hypotension ensued. The presence of bubbles in the RV outflow tract, the pulmonary arteries, and arterioles causes the primary obstruction to RV emptying and left ventricular filling.

In addition to mechanical obstruction to RV outflow, ultrastructural studies of vessels after air embolism in animals have demonstrated endothelial damage at the site of bubble impaction (8). Deposition of platelets, neutrophils, and fibrin as well as lipid droplets are found at the air-blood interphase (8, 9). This fibrin-lipid-platelet mesh may also contribute to the obstruction of flow in the pulmonary circulation.

Other studies (10) have demonstrated that an increase in lung microvascular permeability occurs in a dose-and-duration-dependent manner when air is embolized into the pulmonary artery. Increased permeability was felt to be due mainly to an increase in endothelial barrier permeability as well as to overperfusion of the microcirculation. The return to baseline permeability was proportional to the duration of the embolization. Noncardiogenic pulmonary edema, as seen in our case, or even ARDS has been reported (11). The mechanisms of increased microvascular permeability in air embolism has been studied in sheep, and is believed to be mediated by leukocyte release of superoxide anion (12).

Roentgenographic studies of air embolism have shown pockets of air occurring in the major vessels, cardiac chambers, and pulmonary arteries. Pulmonary artery enlargement and areas of focal oligemia are also seen. Neon washout experiments have confirmed that in the absence of right-to-left shunting, air bubbles in the pulmonary circulation rapidly pass into the alveolar space (13). The pressure gradient between the pulmonary artery and alveolar space acts as the driving pressure for discharge of the intravascular gas into the alveoli. Fortunately, the lung serves as a bubble trap, since only .05 ml of air injected into the arterial system of a dog has proven fatal (14). Paradoxical air embolism can occur in right-to-left intracardiac shunts with catastrophic cardiac and cerebral vascular complications. Recent work (5) has demonstrated that neurosurgery performed with the patient in the seated position may put the patient at risk for paradoxical air embolism, since the normal interatrial pressure gradient frequently becomes reversed in this position.

Treatment. The initial treatment of air embolism is to immediately prevent the entrance of further air into the venous circulation. In one neurosurgical series, the source of air embolism could be found in approximately 50% of cases (14) and discontinuing surgery, as in the case presented, is sometimes necessary if air embolism persists.

Management of the patient in intensive care is primarily directed at maintaining blood pressure and oxygenation. The presence of a mill-wheel murmur will indicate persistence of air in the cardiac chambers, which may also be seen on routine chest x-ray. Durant's maneuver (14)—placing the patient in the left lateral decubitus position—minimizes air egress into the pulmonary vasculature, thereby maintaining RV output. Intravenous fluid administration is also important to help maintain RV output. External chest compression is recommended when the RV has failed and may help break up an "air lock" which has impeded RV outflow. One hundred percent oxygen should be administered; along with improving oxygenation, it has the theoretical advantage of nitrogen washout (air bubbles contain 80% nitrogen). Conversely, if nitrous oxide has not already been discontinued, it should be stopped, because its enhanced diffusion will cause enlargement of air bubbles with adverse effects. Positive end-expiratory pressure may retard air entry into the pulmonary circulation but diminished RV outflow could be a potentially dangerous tradeoff. If ARDS evolves, pulmonary artery catheterization should be performed for optimal management. The use of hyperbaric oxygen has been described, and when available it can ameliorate severe cases (17).

In conclusion, early recognition and treatment of venous air embolism has decreased the morbidity and mortality of this disease. An understanding of the clinical presentation and pathophysiology of this disease allows the intensive-care unit physician to effectively manage this condition.

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Abdominal Pregnancy Causing Massive Lower Gastrointestinal Bleeding: Case Report

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Abstract

This is the report of a case of an abdominal pregnancy eroding into the ileal lumen in which the predominant symptom was massive rectal hemorrhage. Normal radiologic and endoscopy findings resulted in a diagnosis of gastrointestinal bleeding of unknown origin. An emergency laparotomy was performed for persistent hemorrhage and vascular collapse. Resection of the hemorrhagic mass, including 15 cm of terminal ileum, was carried out with good results. No cases of abdominal pregnancy eroding into the small bowel causing lower gastrointestinal hemorrhage have previously been reported in the world literature.

Abdominal pregnancy is a relatively uncommon complication in obstetric practice. The incidence varies widely in different series, from 1 in 3,371 (1) to 1 in 50,820 pregnancies (2). The risk of intraperitoneal hemorrhage due to spontaneous separation of the placenta remains the principal indication for immediate laparotomy (1, 3, 4). Although the initial symptom of abdominal pregnancy is usually abdominal pain, there are several reports of atypical presentations (5, 6). The initial symptom of early abdominal pregnancy in the patient whose case we report on here was massive rectal hemorrhage. Since abdominal pregnancy is never included in the differential diagnosis of lower gastrointestinal hemorrhage, we believe that a detailed case report is merited.

Case Report. A 29-year-old woman, gravida 3, para 3, was seen in the emergency room in August 1981 complaining of moderate epigastric and periumbilical pain and copious rectal bleeding for 24 hours. There was no history of hemorrhoids or diverticular disease or of previous similar episodes. Her last menstrual period had occurred 14 days before. She was hypotensive (blood pressure 80/50 mm Hg). There was tenderness in the right lower quadrant but no guarding or rigidity. No abdominal masses were detected. Rectal examination was painful, especially on the right side. No masses were palpable but fresh blood was present in the lumen. Pelvic examination revealed a slightly enlarged uterus and a palpable right anexal mass, suggesting a right ovarian cyst.

Fluid replacement was commenced immediately (1,500 ml blood and 1,000 ml crystalloid solution). Gastroscopic results were normal and proctocolonoscopy did not detect any lesions other than blood in the lumen. A small-bowel series with barium contrast revealed a mass causing extrinsic compression of the terminal ileum and cecum (Fig. 1). The abdominal and pelvic ultrasonographic finding was a cyst of 12 cm diameter, arising from the right ovary.

In the following eight days, the patient had three episodes of moderate rectal bleeding. A fourth episode resulted in vascular collapse. Blood was transfused and an emergency laparotomy was performed. A hemorrhagic right pelvic mass of approximately 15 cm diameter was

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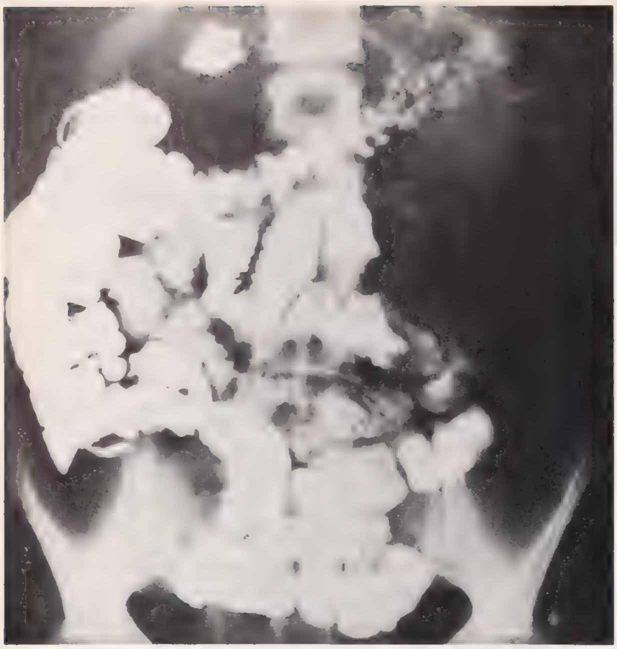

Fig. 1. Barium small-bowel follow-through showing extrinsic compression of terminal ileum and cecum.

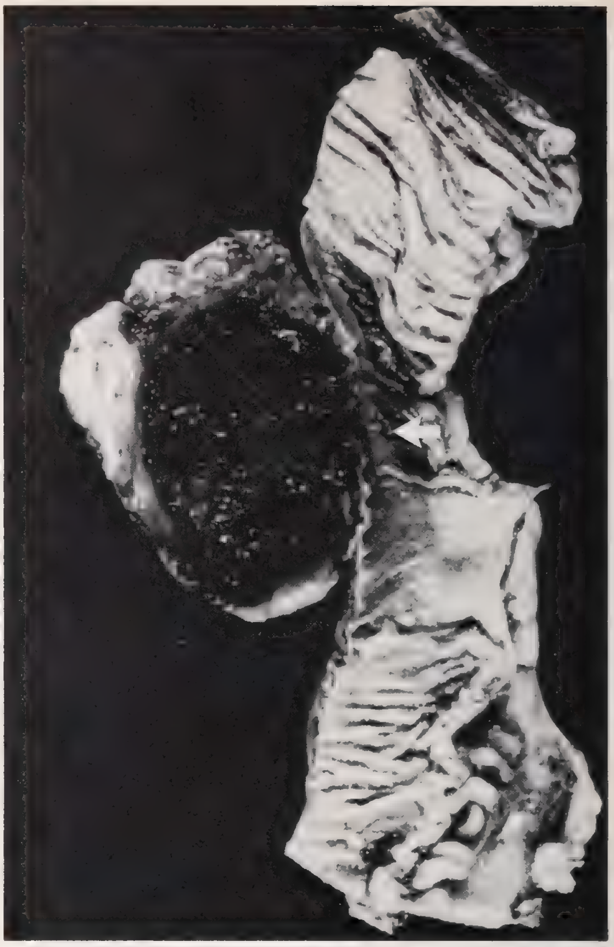

Fig. 2. Mass containing organized blood clots and ileum resected. Both were cut sagitally. Arrow shows opening to lumen.

found. It involved the right uterine tube and the terminal ileum. A separate 7-cm right ovarian cyst was found. The entire mass was resected, including the tube, the right ovary, and 15 cm of terminal ileum (Fig. 2). An end-to-end anastomosis of ileum was performed. Histologic examination showed that the hemorrhagic mass contained organized blood clots with abundant chorionic villi and fetal membranes at various degrees of degeneration (Fig. 3). Its wall was composed of myometrium, fallopian tube (not showing an implantation site), and intestinal wall with a large erosion into its lumen. The pathologic examination yielded the diagnosis of abdominal pregnancy eroding into the ileum. A follicular cyst of the right ovary was an incidental finding.

The postoperative course was uncomplicated and the patient was discharged on the sixth postoperative day. At a follow-up examination four weeks later she was asymptomatic and had returned to work.

Discussion. It is difficult to establish the precise incidence of abdominal pregnancy. An oft-quoted ratio is 1:15,000 deliveries (1, 4, 7). Beacham et al (1) reported an incidence of 1:3,371 in a large series at the Charity Hospital in New Orleans. On the other hand, Rahman (4) reported a rate of 1:10,200, and Tan and Wee's (2) figures from Singapore were 1:50,820. Many factors influence the incidence of advanced abdominal pregnancy; the standard of obstetric care and socioeconomic and racial factors figure prominently (4).

An abdominal pregnancy is designated either primary or secondary according to the assumed site of nidation. Secondary abdominal pregnancy occurs when a fertilized ovum which has begun to develop elsewhere is finally reimplanted in the abdominal cavity. The clinical picture and treatment are the same in both primary and secondary pregnancies. The criteria of primary abdominal pregnancy outlined by Studdiford in 1942 (8) require both tubes to be normal with no evidence of recent or remote injury. Further definitions include the absence of a uteroperitoneal fistula and the presence of a pregnancy young enough (12 weeks) to eliminate the possibility of secondary implantation following a primary nidation in the tube. The abdominal pregnancies that fulfill these criteria are so rare that most authors doubt the existence of primary implantation as indicated by Cavanagh's (9) review.

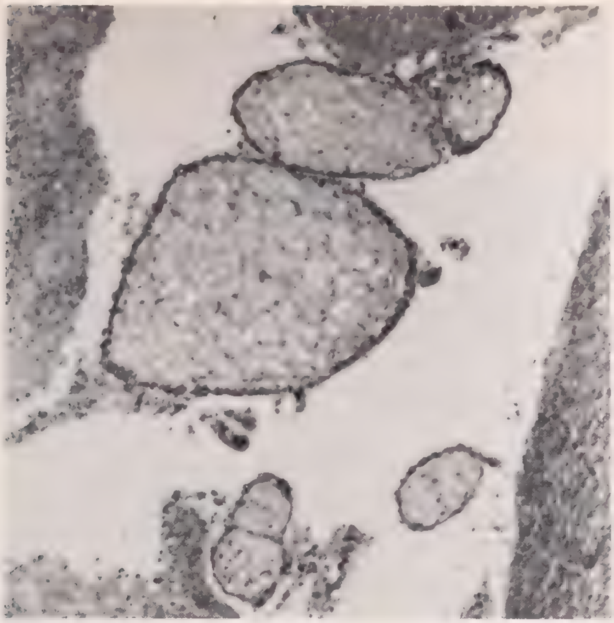

Fig. 3. Histologic specimen showing chorionic villi and red cells taken from mass.

The abdominal pregnancy in our patient was between 5 and 6 weeks gestation. The histologic examination showed that the tube was not the implantation site. The adherence of the tube to the ileum and the pregnancy sac makes it difficult to rule out any previous injury of the tube. Thus we cannot be absolutely certain whether the abdominal gestation was a primary or secondary implantation. The diagnosis was missed because the predominant symptom was rectal bleeding. In addition, the lack of amenorrhea was probably the result of the misinterpretation of the decidual hemorrhage as her last menstruation.

The ultrasonogram was misleading, since it showed only an ovarian cyst which was adjacent to the mass. In more typical cases, the sonographic findings (10) of an empty uterus in juxtaposition to the fetus and placenta, absence of the uterine wall image, and close apposition of fetal parts to the maternal abdominal wall constitute the signs of abdominocyesis. In the case presented here, the pregnancy was too early for a fetus to be delineated on the sonographic examination.

Once the diagnosis of abdominal pregnancy has been made, laparotomy should be performed as soon as possible (1, 4), although close observation in the hospital may be considered (1) in some cases to satisfy the desire of the mother to reach fetal viability. Nevertheless, intraperitoneal hemorrhage from spontaneous separation of the placenta is an unpredictable risk (4); Beacham (1) reports 90% perinatal mortality and 6% maternal mortality due to this cause. The bleeding is related to lack of constriction of the hypertrophied open vessels exposed at the time of placental separation.

No cases of abdominal pregnancy eroding into the small bowel causing lower gastrointestinal hemorrhage have previously been reported in the world literature. In some cases of advanced abdominal gestation with fetal death (3) the gestational sac may be colonized by bacteria, especially when the sac is adherent to loops of intestine; subsequent perforation may lead to elimination of fetal parts per rectum. Because the dominant symptom in our patient was massive rectal hemorrhage, she was investigated from a gastrointestinal point of view. The normal results of radiologic and endoscopic studies led to a diagnosis of gastrointestinal bleeding of unknown origin.

Unequivocal evidence of a bleeding site can only be demonstrated by direct endoscopic or surgical visualization or by extravasation of contrast material at angiography.

Location of the site of bleeding from the gastrointestinal tract may be difficult at times. The history and clinical picture remain the mainstay of diagnosis. Endoscopy has proven invaluable in upper and lower gastrointestinal hemorrhage (11–13). Selective angiography is also of value, provided the bleeding occurs at a rate in excess of 0.5 ml/min (14); scans are more sensitive when bleeding occurs at a lower or intermittent rate (15, 16). Laparotomy may become a diagnostic procedure but may also fail to localize the source of hemorrhage (17). When localized by surgery, however, the bleeding can be corrected.

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Recurrent Nephropathy Associated with Heroin Use

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Abstract

Heroin addicts have been reported to develop glomerular sclerosis and progressive renal insufficiency. The pathogenesis of this lesion has not been determined, and the observation has been disputed. We report a patient, followed for 10 years, who developed relapsing nephrotic syndrome after intermittent heroin use. Although the first and second kidney biopsies showed minimal glomerular change, the third kidney biopsy showed granular, mesangial IgM deposits on immunofluorescent microscopy. Mild diminution of renal function was also seen. Heroin use, in this patient, can be directly related to episodic nephrotic syndrome and a slowly progressive glomerular disease.

McGinn and associates described nephrotic syndrome and progressive renal failure as a complication of intravenous heroin use in 1970 (1). Other workers found the most commonly associated renal disease to be focal glomerular sclerosis although lesions such as minimal change nephrotic syndrome have also been reported (1–3). Heroin nephropathy usually results in rapid deterioration of renal function (1). Occasionally, stabilization or improvement in renal function is seen (3). We report a patient in whom intravenous heroin use appears to have repeatedly provoked nephrotic syndrome.

Case Report

A 33-year-old black man had begun to inject heroin 12 years previously. In October 1971, he was admitted to The Mount Sinai Medical Center with anasarca, proteinuria, and weight gain. Urinalysis showed no cellular elements. Three grams of protein were noted in a 24-h urine collection. Electrolytes were normal, serum albumin was 0.9 gm%, and cholesterol was 379 mg%. Creatinine clearance was 120 ml/min. Quantitative immunoglobulins showed IgG of 620 mg%, IgA of 390 mg%, and IgM of 570 mg%. ANA, ASLO, and HBSAg were negative. An intravenous pyelogram showed normal-sized kidneys. A percutaneous kidney biopsy showed minimal histopathologic change on light microscopy, and electron microscopy revealed foot process fusion of glomeruli. The patient was treated with prednisone and stopped using heroin. The edema abated, he lost 14 lbs, and urinary protein excretion decreased to 1.6 gm/day at discharge 1 month later.

The patient did not return for a follow-up visit. He was incarcerated in January 1972 during which time he claims not to have taken heroin. Edema was not present; protein dipstick urinalysis was negative.

Upon release from prison in June 1972, the patient began to use heroin again. He was admitted twice that year for nephrotic syndrome. A repeat kidney biopsy was performed in December 1972. On light microscopy, five glomeruli were normal and one was obsolete. Tubules were unremarkable; electron microscopy revealed slight focal wrinkling of glomerular basement membranes and obliteration of foot processes.

The patient was lost to follow-up but later claimed to have stopped using heroin. He had no complaints of edema or weight gain. During an admission for alcoholic pancreatitis in 1975 serum albumin was 3.5 gm%, cholesterol was 185 mg%, and urinary protein on dipstick was negative.

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The patient was readmitted in February 1981 with swelling of the legs and face, 15-lb weight gain, and proteinuria after 4 months of intravenous heroin use. Twenty-four-hour protein excretion was 3.6 gm/day. Serum electrolytes were normal. Serum albumin was 1.7 gm%, and cholesterol was 371 mg%. Creatinine clearance was 80 ml/min. Immunoglobins were unchanged from previous values.

In a third kidney biopsy performed 10 years after the first, five glomeruli were seen. There were no changes on light microscopy. However, direct immunofluorescence revealed scattered granular mesangial IgM deposits in the absence of IgG, IgA, C3, and fibrinogen (Fig. 1), and electron microscopy showed a few dense mesangial and subendothelial deposits (Fig. 1).

The patient was placed on prednisone, his edema diminished, and proteinuria decreased to "trace" on dipstick urinalysis. He was then lost to follow-up.

Discussion

This patient, followed for 10 years, had three discrete episodes of intravenous heroin use which were followed by nephrotic syndrome. Cessation of drug use along with steroid therapy led to resolution of the syndrome on three occasions. However, kidney biopsies showed progression of disease. The first specimen was normal on light microscopy, and on electron microscopy only foot process fusion was observed. The second specimen showed one obsolete glomerulus out of six. The third specimen disclosed small mesangial and subendothelial deposits on electron microscopy and granular mesangial IgM deposits on immunofluorescent microscopy.

Immunofluorescent staining for IgM and C3 in areas of glomerular sclerosis of renal biopsies from heroin addicts (1) suggests that lesions identical to the one seen in this patient precede glomerular sclerosis. Moreover, in patients with id-

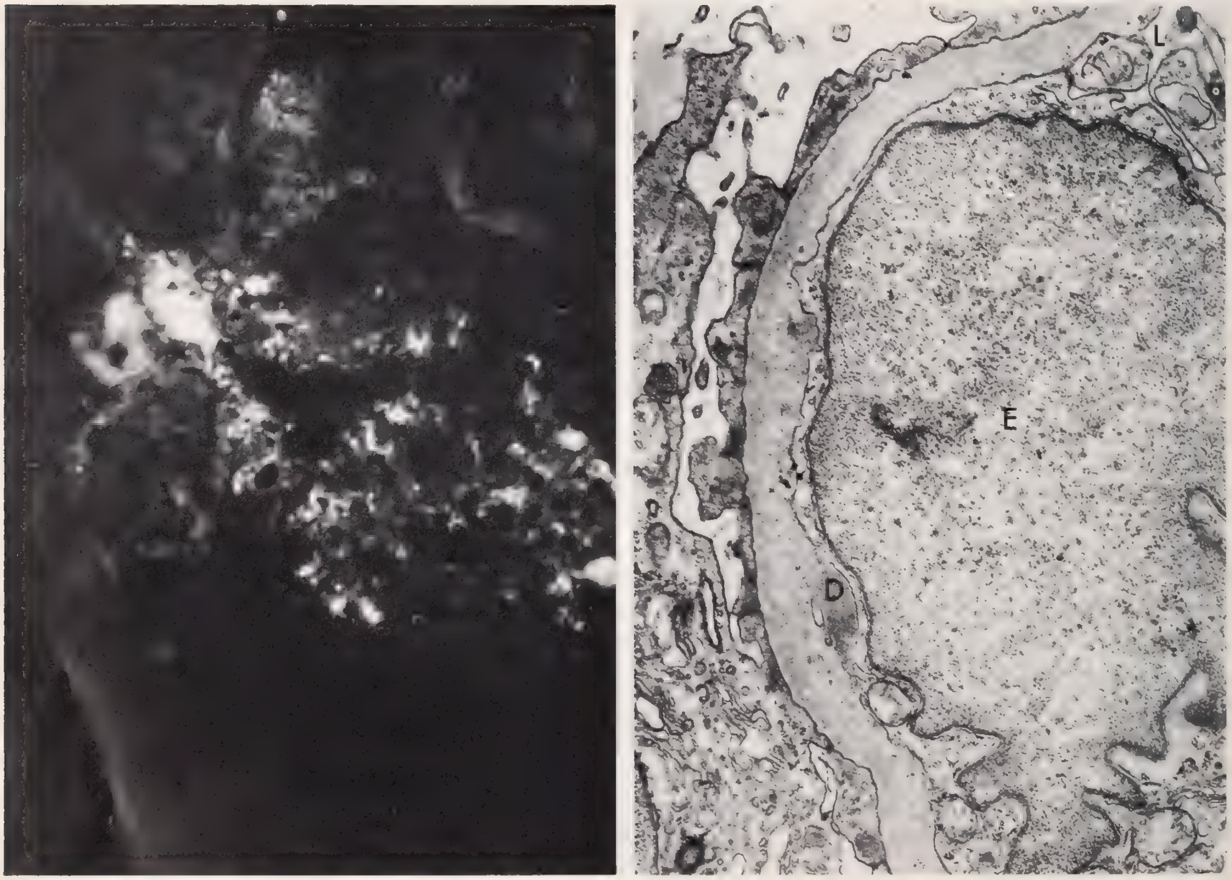

Fig. 1. Third percutaneous kidney biopsy. **Left** Direct immunofluorescence for IgM reveals granular staining of the glomerular mesangium (25× magnification). **Right** Electron microscopy of a glomerular capillary shows a small dense subendothelial deposit (D) (uranyl acetate and lead citrate, 4000× magnification).

iopathic nephrotic syndrome, mesangial IgM deposits with minimal glomerular change are thought to progress to focal sclerosis (4). Experimental evidence for similar progression is seen in the albino rat, which develops focal glomerular sclerosis with IgM deposition in areas of sclerosis at 1 year of age. Glomeruli show mesangial IgM deposits in these rats at ages 3 and 6 months (5). The lack of advancement to glomerular sclerosis in the patient reported here may be related to the sporadic nature of his addiction.

The relationship of glomerular sclerosis to heroin use has been debated (2), and epidemiologic evidence for such an association has only recently been presented (2). In this patient, heroin use appears directly related to the recurrent nephrotic syndrome, diminution in renal function, and the slowly progressive, glomerular histopathologic change.

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Aggressive Juvenile Fibromatosis

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The fibromatoses are a group of pathologically similar and clinically diverse lesions. In children they encompass a number of entities, including juvenile aponeurotic fibroma, fibromatosis colli (sternocleidomastoid tumors), fibrous hamartoma, desmoplastic fibroma, multiple congenital and multiple generalized fibromatoses (1–3).

Stout (4) defined the more specific subheading of juvenile fibromatosis as a tumor that does not fit into any of the above categories and has well-differentiated spindle cells, no anaplasia, few mitoses, little pleomorphism, considerable collagen or reticulin between cells, and is first manifested in persons under the age of 16 years. Although histologically benign, these lesions tend to infiltrate soft tissues and adjacent bones—thus the term "aggressive" juvenile fibromatosis (5).

Case Report

A girl aged 2 years 7 months was admitted for evaluation of a right-sided jaw mass which had been present for at least three months. The mother stated that the mass had not noticeably increased in size during that period.

On physical examination, a $5^1/_2 \times 3^1/_2 \times 2$ cm firm, nontender mass overlying the mandible was palpated. Physical examination was otherwise normal and the child appeared well. Laboratory values were normal.

Roentgenograms showed an aggressive destructive lesion with coarse spiculated periosteal reaction (Fig. 1). The differential diagnosis included Ewing's sarcoma, metastatic neuroblastoma, osteosarcoma, Burkitt's lymphoma, and actinomycosis. A transoral biopsy showed a lesion composed of well-differentiated fibroblasts with slight pleomorphism and rare mitoses, in a myxomatosis stroma with focal collagen formation (Fig. 2).

Aggressive fibromatosis was diagnosed, with low-grade fibrosarcoma mentioned as an unlikely possibility. A postbiopsy computed tomography scan dramatically revealed the size of the lesion and tremendous degree of destruction (Fig. 3). These findings ruled out the presence of an intraosseous desmoplastic fibroma which may be histologically similar to soft-tissue fibromatoses (6).

Discussion

The present case illustrates the difficulties in dealing with fibromatoses in children. Wide excision is the treatment choice, but the tumor may infiltrate 2 to 3 cm beyond its palpable margin; thus, there is a recurrence rate of up to 47% (2, 7). Yet primary and recurrent tumor can lead to deforming surgery, and the disease may cause death by infiltration of vital structures.

Aggressive fibromatosis must also be differentiated from desmoplastic fibroma, which may have a similar histologic appearance (6). The latter tends to remain intraosseous and is more easily resected. While the head and neck are common sites for fibrous tumors in children, involvement of the jaw, as in this patient, is uncommon (2, 5, 7). These tumors may increase rapidly in size or may remain clinically stable for several months, as in the present case. The radiographic appearance of bone destruction, periosteal reaction, and soft-tissue mass may be seen in actinomycosis, but the lack of systemic signs, sinus tracts, fistulae, and fever was against actinomycosis or other infections. Burkitt's lymphoma, osteosarcoma, Ewing's or metastatic neuroblastoma may be suggested on the radiographs but the coarse, widely spaced thick spicules of periosteal new bone are not seen in these lesions and may be characteristic of juvenile fibromatosis (8). Also, the lack of both pain and growth for a period of three months would be unusual with

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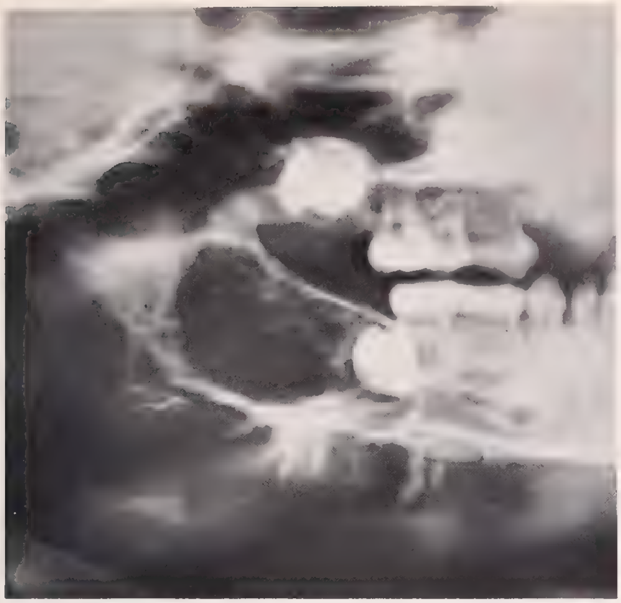

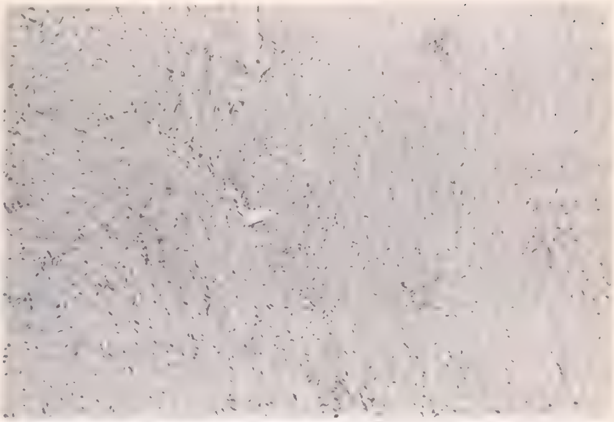

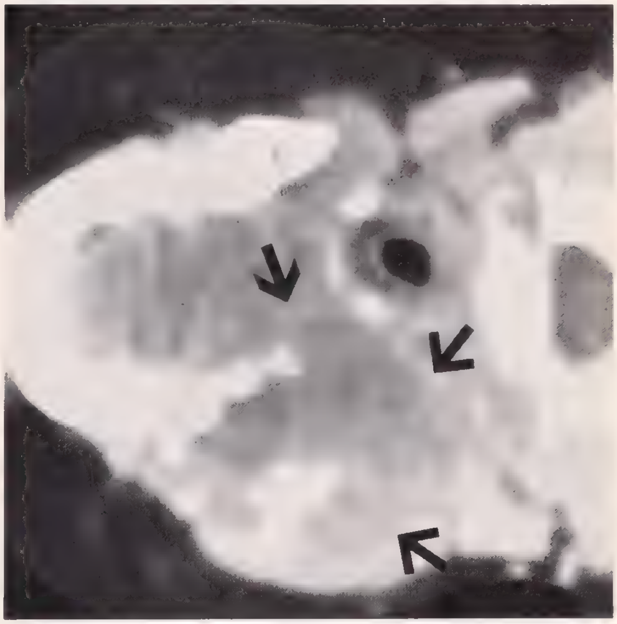

Fig. 1. Top left Panorex of mandible showing lytic lesion with peripheral septae and course spiculated periosteal reaction; slight expansion and loss of smooth cortical line inferolaterally.

Fig. 2. Top right Low-power view of lesion showing spindle cells, collagen, and scattered blood vessels.

Fig. 3. Bottom right Postbiopsy CT scan showing expansion and destruction of mandible with large soft component (arrows). Airway is displaced to left.

these tumors and there was no evidence of another primary neoplasm.

Histologically, the lesion was composed of well-differentiated fibroblasts with slight pleomorphism and rare mitoses, in a myxomatous stroma with focal collagen formation (Fig. 2). Low-grade fibrosarcoma was mentioned as an unlikely possibility in the pathology report; some difficulty in differentiating the two lesions is not unusual (1, 3, 5, 7).

Following the biopsy result, a CT scan dramatically revealed the size of the lesion and the tremendous degree of destruction of the mandible (Fig. 3). With this information, and because of the considerable deformity that would result from extensive surgery or radiotherapy, it was elected to first treat the patient with vincristine and actinomycin D. The tumor has responded by decreasing significantly in size. The patient will undergo reevaluation with the hope that curative surgery will become feasible with less residual deformity.

Although juvenile fibromatosis is considered a benign lesion, its propensity to infiltrate leads to a high recurrence rate. The treatment may involve mutilating surgery, and failure to eradicate the lesion may result in death.

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Brain Biopsy: Risks, Benefits, and Indications

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Brain biopsy has been employed for some time to investigate cerebral disease of unknown origin (1–7). Only a limited number of studies have been undertaken, however, to assess the diagnostic efficacy of the procedure and to evaluate its propensity to produce morbidity and mortality compared to its potential to significantly alter the course of management in a particular case. We review these aspects of brain biopsy and address the question of whether it is indicated in various clinical circumstances.

Diagnostic Efficacy. In 1959, Blackwood and Cumings (1) submitted their review of 65 cerebral biopsies performed on patients of varying ages with progressive dementia. A definite diagnosis was achieved in slightly over half the cases in their early series, thus signaling the arrival of the diagnostic brain biopsy as an important clinical tool. A subsequent expansion of their study (2) to include 178 patients yielded somewhat less efficacious results (43% diagnostic accuracy), as did the studies reported by Wagner and Wisotzkey (3), Eadie (8), Biemond (9), Groves and Moller (4), Moosy (10), and Kaufman and Catalano (7), in which a total of 302 biopsies yielded definite diagnoses in 34.4% of cases. Studies focusing on children (5, 6, 11) have found diagnostic efficacies ranging from 13% to 40%.

To evaluate the relevance of these statistics, it is necessary to focus on the specific diagnoses made as a result of the procedure. In this regard, only the most recent studies appear valid for contemporary practice, since the development of noninvasive diagnostic methods has increased in recent years. Thus, computerized axial tomographic (CAT) scanning may now detect multi-infarct dementia (including Binswanger's disease) and Huntington's disease (marked by caudate atrophy), and a diagnosis of multiple sclerosis is now aided by detecting oligoclonal bands in the cerebrospinal fluid and by demonstrating abnormal visual and brainstem auditory evoked potentials. Similarly, less drastic tests can now give a diagnosis in cases of metachromatic leukodystrophy, subacute sclerosing panencephalitis, and Tay Sach's disease. The trend toward noninvasive diagnosis is likely to continue with the development of newer imaging devices, such as nuclear magnetic resonance (NMR) and positron emission tomography (PET), which may allow tissue-free diagnosis for cerebral mass lesions and for degenerative conditions such as Alzheimer's disease and Pick's disease.

In the most recent review of diagnostic brain biopsy (7), data on 46 procedures carried out over a 12-year period were reported. A clear diagnosis was achieved in 17 cases (37%). Of these, eight consisted of entities known to be invariably fatal and without genetic significance (Alexander's disease, Jakob-Creutzfeldt disease, and congenital laminar misdevelopment); 2 were demyelinating conditions (Schilder's disease and multiple sclerosis); and 7 were varieties of encephalitis. In 22 cases, abnormalities were found (neuronal degeneration, white matter degeneration, astrocytosis, meningeal thickening) but no diagnosis was made. To interpret these results with regard to the value of the procedure employed, a comparison of the risks of the procedure with the potential benefits to be derived is necessary.

Risks of Cerebral Biopsy. Unfortunately, little serious attention has been paid to this aspect of the surgical procedure. It is often stated that cerebral biopsy contains little or no risk (2, 12) but

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a review of the cases shows this to be untrue. For example, Kaufman and Catalano (7) recorded a 13% morbidity and mortality rate in their series of 50 cases. In other reports, transient hemiparesis (4, 6, 9), seizures (12), intracerebral hemorrhage (10, 13), and subdural hematoma (14) have been reported. The procedure is clearly capable of producing serious complications, and this should be weighed when considering the course of management in a particular case.

A further consideration which, to our knowledge, has not previously been addressed is the possibility that removal of brain tissue (usually taken in a block of approximately 1 cubic centimeter volume) from an already cerebrally compromised patient may induce long-lasting cognitive and other behavioral impairments. This possibility is compounded by the potential effects of general anesthesia on the brain-damaged patient. No studies appear to have been directed toward this issue. Its importance is increased when we recognize that regions of the brain previously considered to be "silent areas" (7, 15), such as the right frontal and temporal association cortices in a right-handed person, are actually quite important for normal behavioral function, often in nonverbal activities that may elude cursory evaluation (16, 17). A need is clearly present for careful presurgical and postsurgical neurobehavioral evaluations in patients undergoing diagnostic cerebral biopsies.

Role of Brain Biopsy in Dementia. Twenty-five years ago, the development of the electron microscope and sophisticated biochemical techniques stimulated the use of cerebral biopsy in the management of dementia (18). But when the ultrastructural features of entities such as Alzheimer's and Jakob-Creutzfeldt diseases became known and no specific biochemical abnormalities were found, the use of cerebral biopsy in dementia management declined. Torack (18) reviewed the justification for the procedure in cases of adult dementia and questioned its value. In virtually no cases did it appear that the results of cerebral biopsy altered a patient's management in a way that changed the course of the underlying disease. He focused on three more indirect objectives: analysis of neurotransmitters, establishing prognosis, and identifying pathogeneses.

The importance of neurotransmitters is clearest for dementias of the Alzheimer's type. Postmortem analysis of tissue in Alzheimer's patients has demonstrated a 90% decline in activity of choline acetyl transferase, the synthetic enzyme for acetylcholine (19). It is likely that other neurotransmitters are also important in this disease (20). The argument is advanced that brain biopsy is the only means to provide tissue that is adequate for the assay of the more fragile transmitters, such as the catecholamines. It is possible, however, to obtain important information pertaining to neurotransmitters even from postmortem tissue, provided that the study is performed soon after death and that the head is packed in ice until the procedure is performed (21).

The use of cerebral biopsy in establishing prognosis in demented patients is supported by a report of 29 biopsies for which follow-up information was available in 25 cases (22). It was found that the seven patients who had normal biopsies had much longer survival times than did patients in any of the other diagnostic categories. The use of the procedure in this way is of unclear value, however, when the potential risks are considered, and when it is noted that the prognostic percentages were derived from a small number of cases.

The third objective considered was the possibility of gaining insight into the pathogenesis of the disease. As an example, a patient in whom congophilic angiopathy was diagnosed by biopsy was presented (23). An autopsy study performed eight days later showed a sharp increase in amyloid deposition, demonstrating a surprisingly rapid disease evolution that would have been missed if the preterm biopsy had not been performed. It is plausible that cerebral biopsy might shed light on pathogenesis in other situations, but this must be weighed against the possibility of a complication attributable to the procedure itself.

A special consideration arises when cerebral biopsy is employed to diagnose Jakob-Creutzfeldt disease. Although this entity has a number of typical clinical features (24), including rapid progression, myoclonus, visual agnosia, and motor involvement, and may have a characteristic electroencephalogram, the diagnosis cannot be made with certainty without examination of cerebral tissue. Cerebral biopsy in such cases, however, contains risk for individuals other than the patient. There has been apparent human passage of the disease by means of a corneal transplant (25) and via a contaminated electrode (26). Transmission seems to require direct contact with infected tissue, including lymph nodes and blood in addition to brain (27). Intact skin protects against infection, but an abraded skin surface may offer a portal of entry (18). Since the organism is very resistant to destruction, special sterilization techniques must be employed. Gadjusek et al (28) recommend immersion in 5% sodium hypochlorite solution and autoclaving for one hour at 121°C and 20 psi. Cook and Austin (29) recommend similar precautions for familial cases of Alzheimer's disease, which have also been argued to be transmissible.

Intracranial Mass Lesions. The role of diagnostic biopsy in the case of an identifiable mass lesion is more straightforward. Although angiography, CAT scanning, and NMR imaging often give the clinician a strong indication of the type of lesion present, a tissue diagnosis still remains necessary in most cases before definitive therapy can be recommended. Thus, radiosensitive neoplastic lesions (such as lymphoma) must be distinguished from clear surgical lesions (such as meningioma or abscess) and from infective foci (such as toxoplasma lesions). This last item has become especially relevant with the recent appearance of acquired immune deficiency syndrome (AIDS) in epidemic proportions (30). Moskowitz et al (31) reviewed the biopsies from seven individuals with AIDS. Toxoplasmic encephalitis was diagnosed in five patients, tuberculosis in one, and no diagnosis was achieved in the last patient. Since failure to diagnose and treat toxoplasmic encephalitis promptly may result in unnecessary mortality, the role of cerebral biopsy in these patients is strongly supported.

Suspected Herpes Encephalitis. The role of cerebral biopsy in the diagnosis and management of suspected herpes simplex encephalitis stands as a controversial issue (32–40). The primary argument in favor of the use of biopsy is that it is the only way to make an unequivocal diagnosis, and that diagnostic certainty that allows avoidance of inappropriate treatment with dangerous agents. Griffith and Ch'ien (40), in their review of the subject, discuss the diagnostic value of antibody determinations, electroencephalogram, computed tomographic scans, and radionuclide brain scans, but conclude that direct examination of biopsy tissue is required for definitive diagnosis. They point out, however, that almost one-half of the biopsy specimens examined from patients suspected of having the disease are normal (35).

Vidarabine (9-beta-D-arabinofuranosyladenine), an inhibitor of DNA synthesis, is the recommended agent for treatment of herpes simplex encephalitis. The complications of therapy with this drug include nausea, vomiting, weight loss, weakness, megaloblastosis, phlebitis, and tremors (41–43). Studies investigating the effectiveness of vidarabine in herpes encephalitis have supported its effectiveness (35) provided that treatment is started early. Newer agents (Ara-A-5-phosphate; acyclovir) are also being evaluated and preliminary data are promising.

The difficulty arises, however, when a comparison of the risks of therapy and the risks of cerebral biopsy is attempted. Barza and Pauker (32), for example, undertook a statistical analysis of the subject and concluded that brain biopsy is likely to be the optimal approach in the majority of patients. Their analysis, however, considered as complications only those side effects "serious enough to be equated with death." In contrast, Caplan (37) argued that complications such as altered intellectual function and development of temporal-lobe seizures might be underestimated since these may be features of the disease itself. This issue remains a difficult one, and will require further investigation for resolution. In the meantime, the suggestion of Morawetz et al (39) that the surgery be performed in centers where viral diagnosis can be made and appropriate neurosurgical intensive care can be provided should be followed.

Conclusions. The role of brain biopsy has continually changed during the past 30 years, and it has always been a source of controversy. Several points emerge following our review of the pertinent literature:

(1) Brain biopsy finds its clearest indication with definable focal mass lesions that are surgically accessible.

(2) There is a critical need for systematic evaluation of the long-term effects of the procedure on intellectual and emotional function, and of its propensity for inducing epilepsy.

(3) Exquisite care should be exercised when a case of suspected Jakob-Creutzfeldt or familial Alzheimer's disease is involved.

(4) Studies should be performed only in centers where adequate analysis of the tissue can be obtained, and where appropriate neurosurgical intensive care is available.

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Profile of a Successful Hospital Clinical Parasitology Laboratory

Russell M. McQuay, Ph.D.

The key words to describe a successful parasitology laboratory are motivation/devotion, patience/patients, microscopic skills/excitement, proper collection and handling/endurance, but not necessarily in that order.

Our departmentalized laboratory was the result of the ingenuity and far-sighted plans of the late, venerable pathologist Israel Davidsohn, M.D. Through his efforts, a separate professional services facility was built—more than 32 years ago.

Historically, the Parasitology Division of Mount Sinai Hospital Medical Center has enjoyed national and international recognition. It was begun in 1953 on a modest scale to serve the immediate needs of the hospital and its clinics.

The Patient Population. Two population groups that migrated to Chicago after World War II initially benefited the most: Jewish refugees from Europe who had been in tropical and subtropical countries, and thus had high levels of parasitic infection, and the masses of blacks who migrated from the rural South.

In 1957 the patient load shifted from clinic patients to private outpatients, and this configuration still holds. Although some of these outpatients have been people who have spent some time in the tropics and subtropics (where parasitic problems abound)—as travelers, Peace Corps workers, businessmen—the largest population groups, measuring in the tens of thousands, have been foreign missionaries (1, 2) and their families, who have had assignments in virtually every tropical and subtropical country in the world. After completing about 5 years of service abroad, they have returned to the United States and have been directed by physicians to come to the Parasitology Laboratory at Mount Sinai Hospital in Chicago. They have come to be screened for possible parasitic problems from every state and from Canada during their year of furlough from missionary service abroad. Most of these persons or family groups return to the tropics for successive 5-year cycles.

At present, we are testing many Hispanic immigrants, a group which comes primarily from Mexico to the Pilsen District of Chicago (proximal to the hospital campus), which appears to be the funnel of this immigration before dispersion to the megopolis around the southern edges of Lake Michigan. Other immigrant groups, including Vietnamese, have also been screened, but they make up a smaller portion of the groups served by the laboratory.

Procedures. A variety of parasitology procedures are performed, but the majority of these patients are tested for exotic as well as more common parasites of the tropics. Several products of our research have been used as laboratory tools to assist in the diagnosis of amebiasis and filariasis: diphasic charcoal medium (3) for intestinal ameba and flagellates (*Giardia lamblia,* however, cannot be grown in routine culture media); and the citrate-saponin-acid method (4) for demonstration of microfilaria.

In our protocol for outpatients we purge each eligible individual and utilize ameba culturing for each of the fecal specimens collected. Routine tests for stools include direct wet mounts in saline and iodine; modified Ritchie concentration procedures; permanently stained smears (from either Schaudinn's- or PVA-fixed feces, or both); ameba cultures, gravity sedimentation, and, finally, permanently stained smears of PVA-fixed sediment

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from pooled, positive ameba cultures (single patient).

When it became evident that we were to be flooded with specimens with an overwhelming variety and abundance of parasites through these tests, we began distribution (catalog sales) of these materials to medical centers throughout the United States and Canada as well as to groups providing proficiency testing materials.

Teaching. From the earliest years to the present, the staff of our division has been involved in a variety of on- and off-campus teaching programs utilizing our extensive collection of educational materials. Available to any resident in clinical pathology is a no-fee 4-week self-instructional on-campus parasitology program. (Prior scheduling is required.)

Case Reports. Our experience has included a number of interesting cases, and occasionally an exceptional case.

In 1966 a case of congenital malaria at our laboratory (5) was one of the first reported in recent years. Since then a number of cases have been recorded each year in the United States. All cases have involved immigrant women from endemic areas. In our case a 2-month-old girl, born at Mount Sinai to a staff nurse who had come from the Philippines 3 years previously and who had never had malaria or any symptoms related to malaria, was diagnosed as having *Plasmodium malariae*. Reexamination of blood smears on file in hematology revealed very scanty *P. malariae* in the mother's blood. (*P. malariae* is notorious for producing asymptomatic conditions, and the parasites may survive within these individuals for several decades. For this reason, persons known to have or to have had quartan malaria should never serve as blood donors.)

Another malaria problem presented itself several months ago in a very ill private outpatient—a male missionary who had been in Kenya and had been on chloroquine eradication therapy. His was a case of drug-resistant malaria (*P. falciparum*). Another, more suitable antimalarial drug had to be chosen to treat him.

Another fascinating case (6) was that of a 35-year-old male mongoloid who had been treated on repeated occasions in the Dermatology Clinic with various topical medicines for extensive scabs on his body, in particular on his hands and feet, but none of his body surface was free of scabs. Subsequently, skin scrapings were submitted to parasitologic examination, and massive numbers of *Sarcoptes scabiei* of all stages were demonstrable. Norwegian scabies crustosa is indeed rare in our society, but seems to be more prevalent in male mongoloids.

Tapeworms are still a problem. A 5-year-old missionary child (from Peru) was diagnosed as having the rare tapeworm *Inermicapsifer cubensis*.

Far more serious are cases of *Cysticercus cellulosae*. These larval tapeworms develop from each immediately infective egg of *Taenia solium* swallowed by an individual. The embryo, which escapes from the eggshell, moves by means of hooklets to various sites in the body, such as the muscles, the eyes, and particularly the brain. Patients, including children, who have migrated from Mexico and have convulsions should be considered to have cysticercosis, until proven otherwise. We treat an increasing number of such cases.

Hydatid disease, echinococcosis, is another larval tapeworm problem in North America and elsewhere. Dogs (wolves or foxes) harbor the tiny adult worms. Eggs passed in the feces of these animals are immediately infective to humans either by being swallowed in contaminated water or food or by contamination of hands when petting or fondling infected dogs. The embryos within the eggshell emerge and work their way into various tissues. Unilocular cysts are most commonly located in the lungs or liver, or both. Osseous hydatids are in the long bones of the body and the multilocular (alveolar) hydatids in lung, liver, and so on. The multilocular hydatids frequently result in death. Surgical intervention is essential in echinococcosis.

Among our numerous patients infected with fish tapeworm (*Diphyllobothrium latum*) was a middle-aged Jewish woman who prepared her own *Gefilte* fish at home and who was an employee in the dietary department of a prominent Chicago hotel. The hotel management refused to let her work until she was "freed" of parasitic infection. In our consultation with them, we failed to convince them that she was not a health hazard, since neither the eggs in her stools nor the worm itself is infective—and moreover that two intermediate hosts are required and the source of infection is the consumption of infected raw fish. Thus, this worker lost more than a month of work during therapy to eradicate the parasite.

A lump on the breast brought a black woman to the clinic. A biopsy revealed the larva of a tapeworm determined to be a sparganum. The disease, known as sparganosis, is rare in humans, especially in the United States. Adult worms are found in dogs and cats. The first larval stage is in freshwater cyclops. Evidently, this patient swallowed untreated river water (when visiting in Arkansas) containing infected cyclops (7).

With this profile of a successful parasitology laboratory I have tried to show that accompanying the routine have been periods of great excitement. More important is the sense of satisfaction that we at the laboratory have been and continue to be of service to physicians and their patients.

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Radiology Notes

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Interventional Radiology of the Biliary Tree: Introduction

John S. Train, M.D.

In 1974, Okuda et al introduced the Chiba needle, a thin-walled, 23-gauge needle which could be safely inserted percutaneously into almost any location in the body (1). As a result of this advance, many new techniques have been developed and old ones revised.

For example, the use of this needle has changed transhepatic cholangiography (THC) from a procedure with moderate morbidity to an extremely safe and highly accurate technique (2). Also, the ease with which the biliary tree can be opacified provided impetus for the development of other percutaneous therapeutic techniques dealing with the varied problems of the biliary tree.

THC is done under local anesthesia and sedation. Under fluoroscopic observation, the needle is directed slightly above the porta hepatus in the mid-axillary line. Small amounts of contrast material are injected as the needle is withdrawn. Eventually the needle will cross a bile duct and the contrast material will begin to fill the biliary tree. Adequate amounts of contrast material are then injected to define the duct system and demonstrate the site and nature of the obstruction.

A multi-institutional survey of results and complications of transhepatic cholangiography was compiled by Harbin et al (2). The study included 2,000 procedures from 30 hospitals. Bile duct visualization was accomplished in 97.8% of patients with dilated bile ducts and 70.2% of those with nondilated ducts.

The commonest serious complication in the series, occurring in 28 patients (1.4%), was sepsis. Sepsis was defined as fever and chills accompanied by either hypotension, a positive blood culture, or severe prostration. An additional 3% of patients had transient fever.

Intraperitoneal bile leak occurred in 29 patients (1.45%), all of whom had intrahepatic biliary obstruction. Of these 29 patients, 13 developed signs or symptoms of bile peritonitis requiring surgery. In the other 16 patients, bile leak was an incidental finding at subsequent surgery for relief of the obstruction demonstrated by THC. Intraperitoneal hemorrhage occurred in only 7 patients (0.35%), and subcapsular bleeding occurred in 12 patients (0.6%).

Four deaths occurred (.14%). One patient died from bile peritonitis, one from intraperitoneal hemorrhage, and one from septic shock. The fourth patient died one hour following the procedure. The cause of death in this patient was not established.

Other complications included two small pneumothoraces and three reactions to the contrast medium. Approximately 10% of the patients experienced mild to moderate right upper quadrant pain. The pain usually abated within 20 minutes and was felt to be due to extravasation of contrast material under the liver capsule.

Similar complication rates for endoscopic retrograde cholangiopancreatography have been reported in a large series by Bilbao (3). Of 10,000 patients, 3% had serious complications (predominantly sepsis). There were 20 (.2%) deaths.

Harbin et al concluded that as THC and endoscopic retrograde cholangiopancreatography have comparable complication rates, the lower cost, ease of performance, and higher success rate

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make THC preferable for the evaluation of jaundice, except in patients with poor coagulation profiles. Also, the ability to define the biliary tree above the obstruction allows for more accurate planning of the subsequent operation or percutaneous procedure. Finally, an additional advantage is that once visualized, the obstructing lesion, whether it be intrinsic or extrinsic to the biliary tree, can be biopsied with a Chiba needle at the time of THC.

Catheter manipulation of the biliary tree is a logical progression from THC and is an extension of standard angiographic techniques. Once the biliary tree has been visualized by THC, puncture of a dilated duct with a larger needle is usually accomplished without difficulty or significant morbidity. After the bile duct in question is cannulated, various catheters and baskets can be manipulated in position, so that a variety of therapeutic measures can be accomplished. For most procedures, local anesthesia and sedation are sufficient, and patients can usually be discharged 24–48 hours after procedure completion.

The three case reports that follow are examples of the use of percutaneous transhepatic techniques to achieve significant therapeutic goals. These procedures offer low morbidity and a cost-effective approach to problems of the biliary tree.

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Percutaneous Transhepatic Removal of a Giant Bile-Duct Stone

BERNARD LEWIN, M.D., JOHN S. TRAIN, M.D., SOL J. DAN, M.D., AND HAROLD A. MITTY, M.D.

Case Report. A 67-year-old-man, with a history of cholecystectomy, cirrhosis, anemia, and partial gastrectomy for peptic ulcer disease, was admitted with jaundice, cirrhosis, and a retained common-bile-duct stone. Two surgical attempts to remove the stone were unsuccessful due to adhesions from previous operations. Following the last attempt, the patient developed increasing liver failure, with ascites and two episodes of hepatic coma.

As seen in the physical examination, the patient was a thin, elderly man with icterus, gynecomastia, and 2+ pitting edema of the lower extremities.

A transhepatic cholangiogram demonstrated a large stone in the common bile duct (Fig. 1). Percutaneous internal biliary drainage was established, with improvement of hepatic function (Fig. 2). The patient was then discharged with plans for readmission after the percutaneous tract had become well established.

The patient was readmitted six weeks after the initial drainage. The stone was too large to be removed intact. Attempts to fragment the stone were unsuccessful and dissolution with monooctanoin (Capmul 8210, Stokely Van Kamp) was proposed. A pigtail catheter to be used for infusion was placed via the previously established tract into the common bile duct, proximal to the stone. The original catheter was left in place to allow a constant egress for the solution into the duodenum.

The patient tolerated the infusion of 10–15 cc/hr complaining only of mild nausea, which was felt to be due to a slight biliary tract distention. On the sixth day of the monooctanoin infusion, the patient began to vomit and complain of moderate abdominal pain. The infusion was stopped.

Cholangiography at this time revealed that the stone had diminished in size and had fragmented (Fig. 3). A basket was then used through the tract to crush and remove the fragments under fluoroscopic guidance. A repeat cholangiogram two days later confirmed that all fragments of the stone had been removed from the biliary tree (Fig. 4).

Discussion. Nonsurgical approaches to biliary stones have been attempted with varying degrees of success. These include conservative treatment with various oral agents which require from six to twelve months of therapy. These agents, chenodeoxycholic acid and ursodeoxycholic acid, have been effective only with stones within the gallbladder, and are further limited by the length of time required for therapy (1).

Endoscopic retrograde papillotomy has been successfully utilized to remove common-bile-duct stones. However, the technique requires specific skills on the part of the endoscopist and is limited to removal of small stones that can be extracted through the papilla.

Stones retained in the common bile duct after surgery have been removed successfully for years through tracts created by T-tubes left in place at the time of surgery (2). The tract matures within one month of surgery to allow removal, with catheters and baskets, of any retained stones.

Two developments in recent years have made percutaneous treatment of common bile duct stones discovered *de novo* more feasible. The first is the development of fine-needle percutaneous cholangiography and biliary drainage, and the second is the development of agents that are ca-

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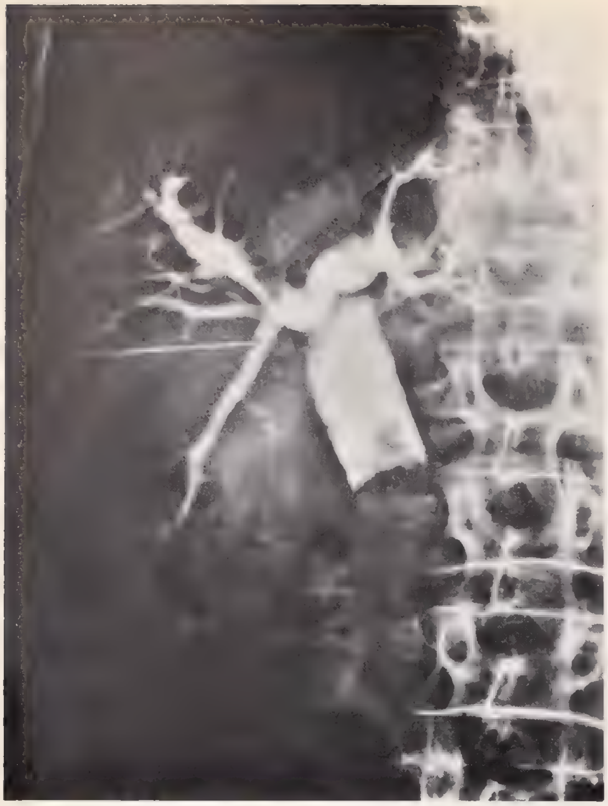

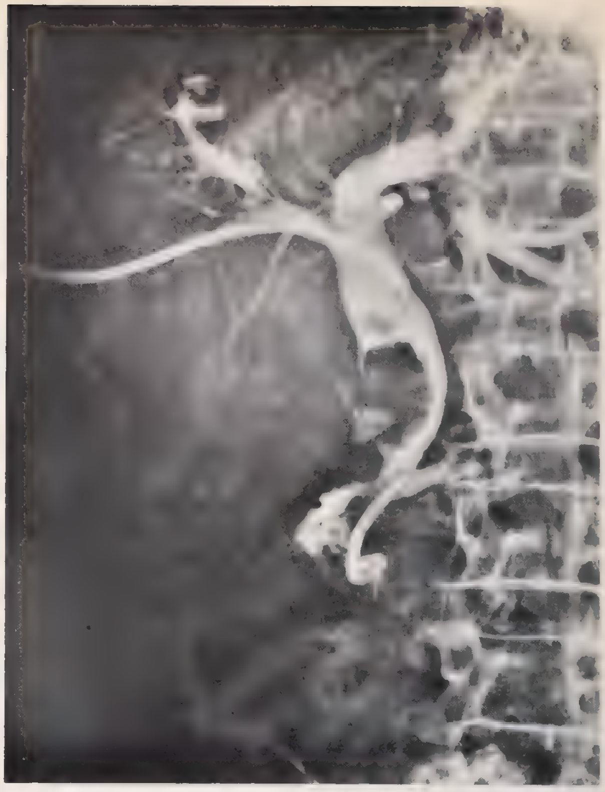

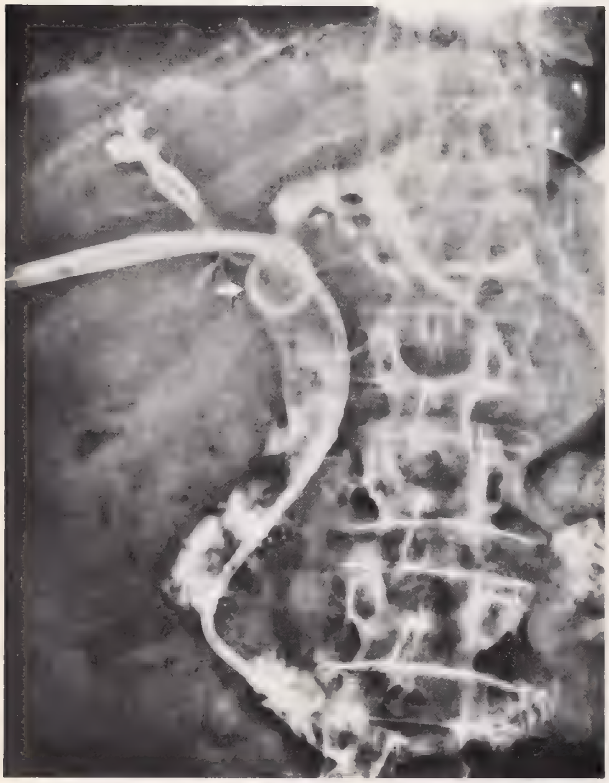

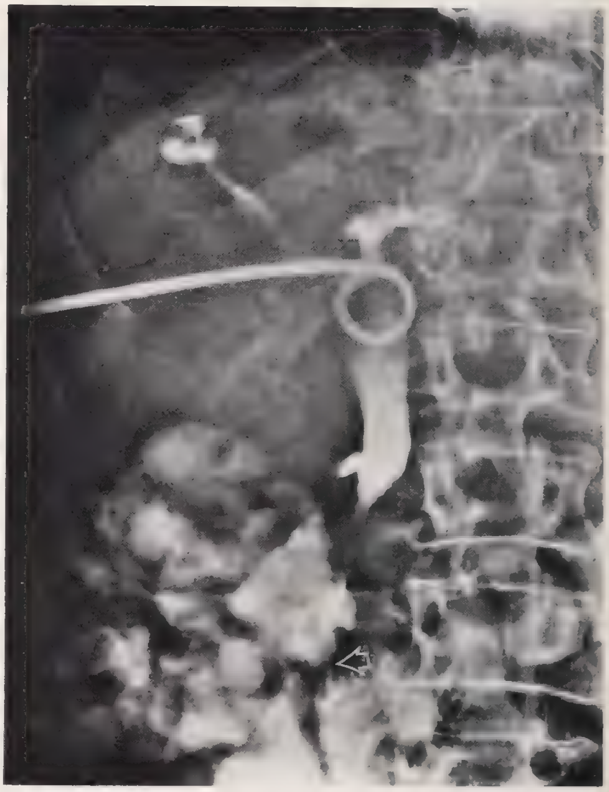

Fig. 1. Top left Transhepatic cholangiogram. Common duct is markedly dilated. Large filling defect is evident in distal duct, obstructing flow of contrast medium.

Fig. 2. Top right Cholangiogram via biliary drainage catheter. Large stone is present in distal common duct. Second, smaller stone is seen more proximally. Drainage catheter is positioned with distal end in duodenum. Antegrade flow of contrast medium through tube into duodenum can be seen.

Fig. 3. Bottom left Cholangiogram via infusion catheter. Second catheter has been positioned in common bile duct for infusion of monooctanoin (arrow). Stone has separated into fragments. These were easily extracted percutaneously.

Fig. 4. Bottom right Cholangiogram via infusion catheter. Drainage catheter and all stone fragments have been removed. There is flow into duodenum (arrow).

pable of dissolving stones when infused into the biliary tree (3–9).

The most successful agent used in stone dissolution has been monooctanoin (Capmul 8210) (6–9). This is a cholesterol solvent that has been shown both in vitro and in vivo to dissolve cholesterol stones (7).

Monooctanoin is a naturally occurring breakdown product of medium chain triglycerides and has been used orally in treatment of certain types of malabsorption in many patients without side effects. It would seem, therefore, that intraductal infusion should be safe.

Infusion of 10–15 cc/hour of monooctanoin over six to eight days into the biliary tree is generally required to achieve effective gallstone dissolution. The infusion has been delivered via catheters placed endoscopically (9) or percutaneously (3, 8) into the biliary tree.

The most frequent side effect of therapy with monooctanoin is nausea, followed by abdominal pain, believed to be due to biliary duct distention (10). This problem can be avoided by placing an internal drainage catheter to allow egress of bile and monooctanoin into the duodenum, thereby preventing overdistention of the biliary tree. Infusion into an obstructed system has been reported to cause systemic symptoms. It has also been reported that prolonged exposure to high concentrations of monooctanoin may cause duodenal ulceration and bleeding (10).

In conclusion, we used the combined techniques of percutaneous biliary drainage, infusion of monooctanoin, and, with a basket, fragmentation and retrieval of a giant retained common-bile-duct stone. We thus successfully managed this obstruction affecting a high-risk patient, for whom surgery would be difficult; the procedure was done under local anesthesia with no significant morbidity.

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Percutaneous Transhepatic Dilation of a Choledochoenterostomy Stricture

Mika Lidov, M.D., John S. Train, M.D., Sol J. Dan, M.D., and Harold A. Mitty, M.D.

Case Report. A 35-year-old woman was admitted with a three-week history of jaundice, icteric sclerae, pruritis, acolic stools, and a ten-pound weight loss. The patient had undergone a cholecystectomy ten years earlier, after which she continued to drain abundantly through her T-tube. Exploratory surgery at that time revealed injury to the common bile duct. She therefore underwent a choledochojejunostomy and did well for ten years thereafter.

The laboratory findings on admission were: alkaline phosphatase 375, SGPT 124, SGOT 37, bilirubin 9.3, U/A 2+ for bilirubin. A transhepatic cholangiogram revealed complete obstruction at the site of the anastomosis (Fig. 1). External and then internal biliary drainage was established without difficulty. The stenotic anastomosis was dilated twice in three days, using a 9-mm balloon catheter (Fig. 2). After dilatation, a 12-French feeding tube was placed as a stent across the treated area and clamped to allow internal drainage (Fig. 3). The patient was discharged, given a prescription for oral antibiotics, and told to return in one month for further dilatation.

She was readmitted one month later, at which time laboratory evaluation revealed normal liver functions. She underwent a third dilatation with a 9-mm balloon catheter. A 12-French feeding tube was again left in place across the dilated stricture, and the patient was discharged on her third hospital day. The feeding tube remained in place for 11 weeks. A cholangiogram after the removal of the tube revealed a free flow of contrast material across the anastomosis (Fig. 4). The patient has remained asymptomatic and has had normal liver-function tests for 18 months.

Discussion. In the last twenty-five years, multiple surgical procedures have been proposed for the repair of biliary strictures, including hepaticogastrostomy, end-to-end repair, Roux-en-Y hepaticojejunostomy, hepaticoduodenostomy, grafts, vitelline stents, and intraoperative dilatations (1, 2). Warren, in reviewing 987 patients with benign biliary stricture that required 1553 operations, reported an overall success rate of 78%, a postoperative morbidity of 25%, and an overall mortality of 13% (1). The prognosis was very much dependent on the number of surgical procedures (1). The first operation had the best prognosis, and a satisfactory result was unlikely if more than three repairs were required. Way, in reviewing 87 patients with benign biliary stricture requiring 128 operations, reported an overall success rate of 65%, but a significantly better result (78%) with hepaticojejunostomy (2); three of 12 patients whose initial strictures were treated by hepaticojejunostomy presented with recurrent stricture.

Apart from these three cases of hepaticojejunostomy, we could find no assessment of repair of strictures specifically in choledochojejunostomy anastomoses. However, since most patients with choledochojejunostomy have had two prior operations, one may surmise that the outcome is at least no better than that reported for primary biliary stricture repair.

Percutaneous transhepatic dilatation of postsurgical biliary stricture was introduced in 1978 by Molnar and Stockum who described nine cases of strictures of choledochoenterostomy successfully treated with this technique (3). Seven of the nine had no evidence of recurrence up to five years following dilatation. Subsequently, this

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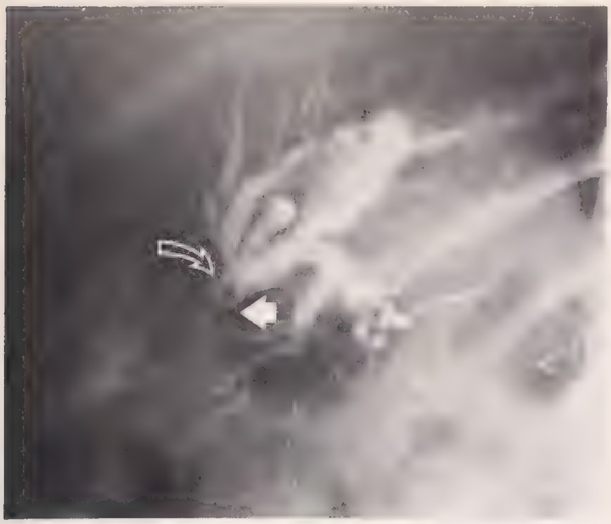

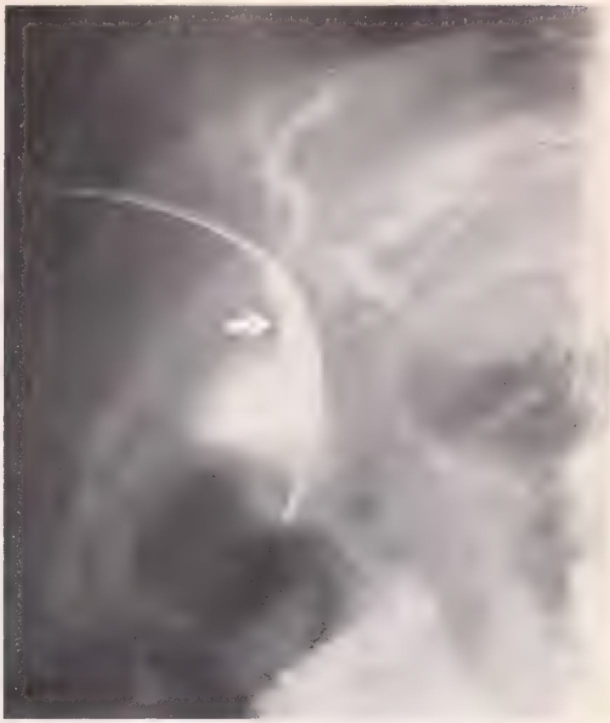

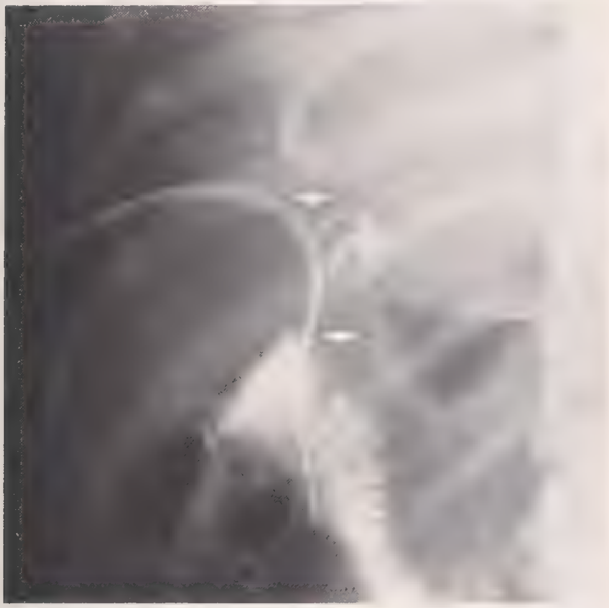

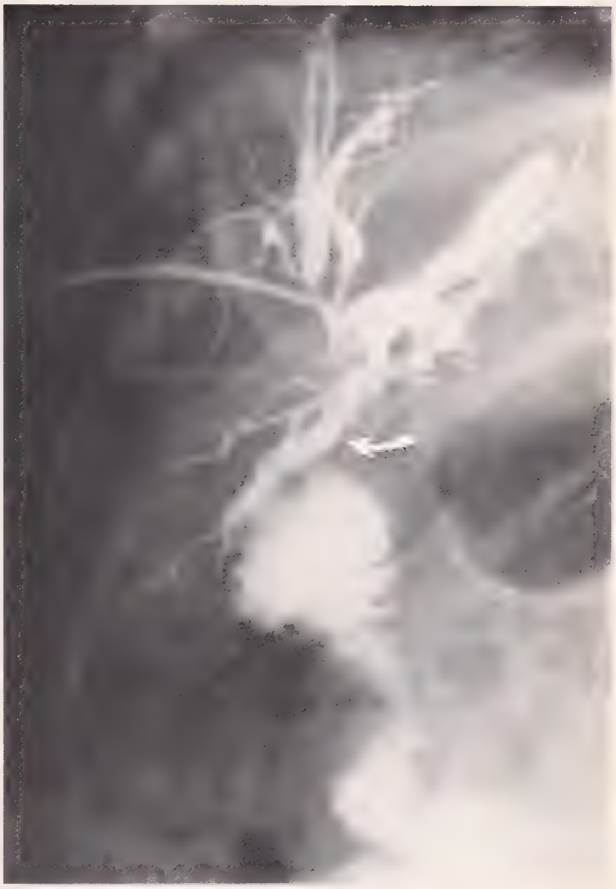

Fig. 1. Top left Transhepatic cholangiogram. There is complete obstruction of choledochojejunostomy (arrow). A radiolucent stone is seen at anastomotic site (open arrow).

Fig. 2. Top right Dilating balloon (9 mm) has been inflated at anastomotic site. Note the "hour glassing" of the balloon indicating the location of the stricture (arrow).

Fig. 3. Bottom left Catheter (12 French) with holes above and below stricture has been positioned so as to stent dilated stricture and provide antegrade drainage (arrow).

Fig. 4. Bottom right Cholangiogram through cutaneous track. There is now good flow into jejunum through anastomosis (arrow).

technique has been applied to biliary strictures unrelated to anastomoses. Martin described two patients with postoperative stricture of the left and right hepatic ducts who were successfully treated with percutaneous dilatation (4). This technique has also been used to treat strictures secondary to sclerosing cholangitis and malignancy (5). However, the report by Molnar and

Stockum on choledochoenterostomy strictures remains the only large series with long-term followup.

Transhepatic percutaneous dilatation is performed in three phases. Initially, external drainage is established in order to allow liver function to return to normal. After several days, internal drainage is attempted by advancing a catheter through the stricture.

Once internal drainage is functioning adequately, the third phase, percutaneous dilatation, is attempted. The drainage catheter is replaced with a balloon dilatation catheter, and the balloon is inflated, expanding the stricture. The dilatation is repeated several times over a period of three to four weeks. Between dilatations, a 12-French feeding tube with multiple side holes is left in place across the stricture to prevent recurrent stricture formation and to provide internal drainage. Note that this third-phase percutaneous dilatation includes several dilatations. That the dilatation is multiple rather than single, as in surgical dilatation, may explain the excellent results reported by Molnar and may be the key to long-term patency. Our patient has remained symptom-free, with normal bilirubin and alkaline phosphatase, for 1.5 years since dilatation.

Percutaneous transhepatic dilatation offers a therapeutic alternative to surgery for the treatment of choledochojejunostomy strictures, without the hazards and complications of reoperation. It is also much more cost effective, can be repeated in the event of recurrent stricture formation, and does not preclude subsequent surgery if dilatation fails.

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Radiology Notes

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Percutaneous Transhepatic Placement of a Biliary Endoprosthesis

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Case Report. A 76-year-old white woman was admitted with the symptoms of painless jaundice, dark urine, and light-colored stool. The results of admission tests showed bilirubin 12.9, alkaline phosphatase 449 (normal 30–110), SGPT 160 (normal 1–53), SGOT 62 (normal 1–50). Ultrasound and computed tomography demonstrated dilatation of the gallbladder, common bile duct, and pancreatic duct. No masses were seen. At laparotomy, a firm mass, 3.5 × 3.5 × 3 cm, was found in the head of the pancreas, causing extrahepatic obstruction of the biliary system. There was no evidence of metastatic disease. A double bypass was performed. Postoperatively, studies of the patient's liver function showed improvement. Six months later, she was readmitted with a recurrence of jaundice, hypoalbuminemia, and ascites. At this time, her bilirubin test value was 4.2 and alkaline phosphatase was 556. Mid-common-bile-duct obstruction was demonstrated by transhepatic cholangiogram and external percutaneous biliary drainage was established. Subsequently, internal drainage was achieved. It was felt that the patient could not tolerate a catheter protruding from her side, therefore, a 12-French biliary stent was passed across the obstruction in the midcommon bile duct into the duodenum (Figs. 1, 2).

Discussion. Operative mortality in various biliary bypass procedures for malignancy has been reported to range from 13% to 21%, with survival rates averaging only 5–7 months after successful surgery (1–3). In cases of extensive metastasis, perioperative mortality and morbidity rates for surgical procedures may approach 59% (1, 4). In addition, surgery implies a longer hospital stay, the need for general anesthesia and an overall increase in cost. In recent years, percutaneous transhepatic biliary drainage has been established as effective and often safer than surgical therapy for obstructive jaundice (5, 6).

Percutaneous transhepatic biliary drainage can be achieved in a high percentage of patients with obstructions. In two recent large series, the overall success rate of percutaneous internal and external drainage procedures ranged between 93.5% and 94% (5, 6).

External drainage is accomplished, following transhepatic cholangiography (THC), by percutaneously placing a catheter with multiple holes through the liver into the biliary tree proximal to the obstruction. Bile will then drain externally. Normal bile flow in adults is approximately 600 ml per 24 hours, with high electrolyte concentrations. Therefore, in patients with external drainage, electrolyte imbalance is a constant concern. Also, the loss of bile may cause depletion of the enterohepatic circulation of bile acids, with resultant malabsorption and malnutrition. Thus, it is important to attempt to establish internal drainage.

Internal drainage can be achieved by manipulating a catheter across the obstructing lesion in the common bile duct into the duodenum, so that multiple side holes lie both proximal and distal to the obstruction. This allows bile to enter the catheter and drain internally past the obstruction into the duodenum. If the catheter is properly functioning, it can be closed externally at the skin. For long-term drainage, we prefer to replace the initial 8.3-French catheter with a softer, 12-French feeding tube, with larger side holes allowing better drainage.

Major periprocedural complications have been

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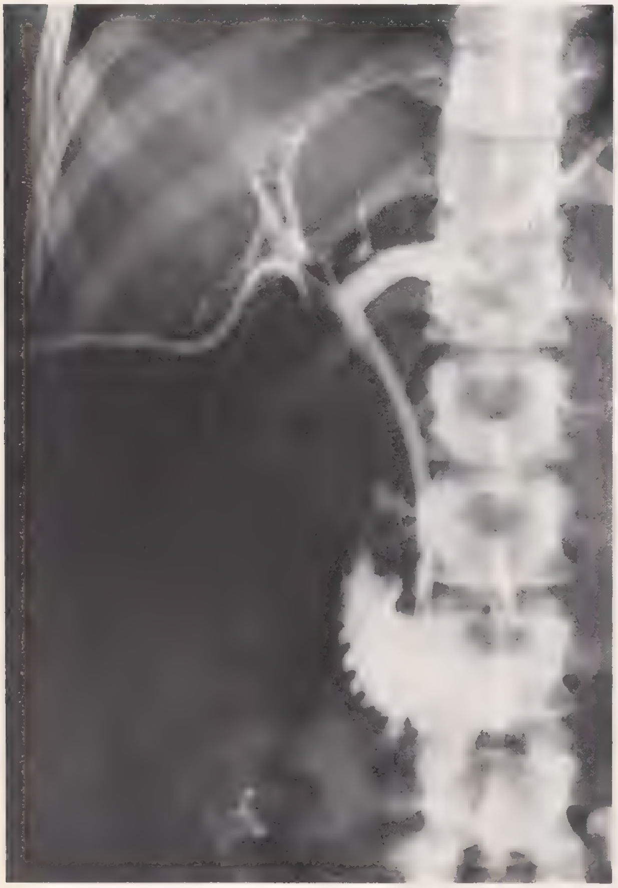
reported to occur in 4.8% to 8% of patients (5, 6). These include septicemia, bleeding, bile peritonitis, and death—3 of 200 in the series reported by Mueller et al (6). Minor periprocedural complications have been reported to range from 19.3% to 20% of patients; postprocedural fever, postclamping cholangitis, hemobilia, and hyponatremia are among these complaints. Chronic problems encountered with percutaneous transhepatic biliary drainage include inadvertent dislodgement of the drainage catheter, infection, as well as the emotional irritation of the visible catheter, which is a constant reminder to the patient of his or her disease. The use of a 12-French feeding tube has decreased the incidence of infection by promoting better drainage (6). The emotional and physical discomfort associated with internal and external drainage, however, is not relieved.

Percutaneous placement of a completely internal stent endoprosthesis eliminates these latter problems. In this technique, a 12-French endoprosthesis stent, with multiple proximal and distal side holes, is pushed through the site of obstruction over a previously placed 8.3-French internal biliary drainage catheter by another segment of 12-French catheter tubing. The inner catheter is then removed, leaving the 12-French stent entirely within the biliary tree and duodenum (Figs. 1, 2). The procedure is done using local anesthesia and sedation, and can usually be accomplished in 4–7 days from the initial THC.

Hellekant (7) described eight patients with inoperable obstructive jaundice in whom an endoprosthesis was inserted percutaneously through the obstruction. Four of the patients were alive 1, 5, 15, and 19 weeks after endoprosthesis placement. The four other patients died after 3, 3, 5, and 26 weeks. In three patients in whom autopsy was performed, the endoprosthesis was patent; however, the liver was massively infiltrated by tumors. In the patient who died at 26 weeks after insertion, a cholesterol calculus was found proximal to the patent stent. This complication could



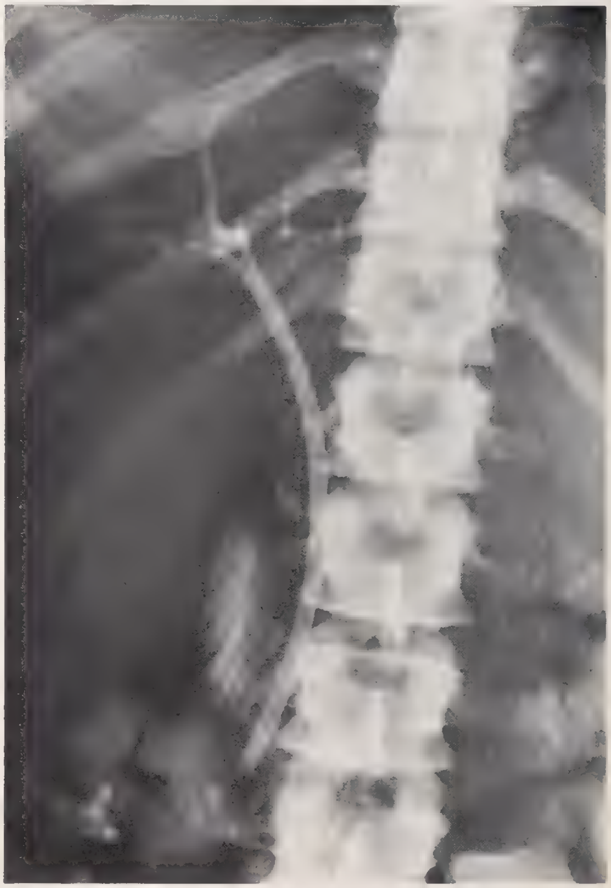


Fig. 1. **Left** Cholangiogram via external drainage catheter. Endoprosthesis has been positioned through obstructed common bile duct into duodenum. Contrast medium injected above prosthesis flows easily into duodenum.

Fig. 2. **Right** External catheter has been removed leaving endoprosthesis in place.

conceivably have been managed percutaneously. In all patients, the serum bilirubin levels decreased after the procedure, and in three, the levels returned to normal.

In a recent series, Teplick et al (8) described 17 patients with endoprosthesis placement. Stent patency was evaluated by obtaining periodic serum bilirubin levels. In 15 of these patients, the bilirubin continued to decrease or remained stable. One patient had no followup tests of bilirubin levels, but remained clinically icteric until she died from disseminated tumor three weeks later. Seven of the patients died from carcinoma or related problems in from 3 to 22 weeks after the procedure (average 10.5 weeks). Nine were still living at the time of the report, having been followed for from 6 to 56 weeks (average 18.5 weeks).

If the endoprosthesis stent is blocked either by tumor or debris, it must be cleaned, or replaced endoscopically, or a new stent must be placed percutaneously. This is the main disadvantage encountered with this technique.

In conclusion, we feel that completely internalized biliary endoprostheses in patients with unresectable lesions causing obstructive jaundice offer advantages over bypass surgery and percutaneous internal biliary drainage with a protruding catheter.

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Student's Corner

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Crohn's Disease and Pregnancy: A Literature Study

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Abstract

Crohn's disease may be defined as a chronic, progressive granulomatous disorder that can affect the gastrointestinal tract from mouth to anus. There has been little documentation of the effects of Crohn's disease on pregnancy. The literature regarding fertility in Crohn's disease suggests that the activity of the disease state at the time of conception is related to the fertility rate. Although pregnancy was not found to have an adverse effect on the course of Crohn's disease, the nature of the activity of the disease during the gestational state had a direct influence on the outcome of the pregnancy. Although a theoretical risk of fetal complications with the use of corticosteroids exists, the benefits alleviating the course of Crohn's disease during the pregnancy outweigh the risks of potential complications from the use of these drugs. Likewise, surgical intervention during pregnancy for fulminant disease activity is indicated when Crohn's disease is unresponsive to medical management alone. Since Crohn's disease affects predominantly child-bearing age groups and is occurring with increasing frequency in women, it is essential that one review the role of inflammatory bowel disease in the gravid state. The application of this knowledge is critical in the management of these patients.

The incidence of Crohn's disease in western Europe and the United States is approximately two cases per 100,000 population (1). The prevalence rate, however, has been estimated at 20–40/100,000 population (2). Furthermore, many believe that the incidence is increasing, although there has been no firm documentation of this.

Though Crohn's disease has been found in all age groups from the neonate to the elderly, it has its peak incidence in the second and third decades of life. In Crohn's original work (3), males were described to be affected twice as frequently as females. Recent studies indicate little difference in incidence between the sexes, and some even show a female preponderance (4).

The etiology of Crohn's disease remains unknown. Several theories have been proposed including infectious (5, 6) and immunological (7, 8) causes. Most recently, a genetic susceptibility has been implicated and studies are now focusing on the HLA typing (9–12). Though a direct relationship has not been shown, it is important to bear this concept in mind when discussing the issue of reproduction with Crohn's patients.

In light of these reports, it is essential to study the relationship of Crohn's disease and pregnancy. Several areas have been examined, including fertility, sterility, the influence of the disease on pregnancy, the influence of pregnancy on the disease and the postpartum period, drug therapy during pregnancy, and the effect of bowel surgery during pregnancy. Various results on these issues have been obtained in the individual studies. The purpose of this paper is to compare and analyze these data and to discuss the implications of these results in the management of pregnant patients with Crohn's disease.

Literature Review

Infertility. The terms "fertility," "infertility," and "subfertility" have been used to describe a woman's potential to become pregnant while afflicted by Crohn's disease. One of the largest earlier series that discussed this issue was that by

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Crohn et al in 1956 (13). These authors reviewed a total of 84 pregnancies in 53 of 133 females and concluded that fecundity was not impaired by Crohn's disease.

Fielding and Cooke (14), on the other hand, found almost one third of the women of childbearing age to be infertile. Furthermore, they found the chances of infertility to be significantly greater in patients with Crohn's colitis than in those with involvement of the small intestine (67% versus 26%; $p < 0.01$). Fielding and Cooke attributed the infertility to the effects of Crohn's disease, that is, to bilateral occlusion of the fallopian tubes by adhesions. Deficiency of vitamin B_{12}, often resulting from intestinal resections, was also considered a potential cause. Several "infertile" patients became pregnant after vitamin B_{12} replacement.

A similar conclusion was reached by DeDombal et al (15) in their analysis of 86 women who had been seen and treated at the General Infirmary in Leeds, England, for Crohn's disease. Forty-six of eighty-six women (54%) were unable to conceive in a follow-up series that was 99% complete. Furthermore, as in Fielding and Cooke's study (14), a larger proportion of these women had colitis rather than ileitis, though no statistical difference existed.

DeDombal et al's study (15) did not term these women infertile but subfertile. This was based on their finding that after surgery for Crohn's disease, the chance of a patient becoming pregnant approached that of the general population. Thus, women were only temporarily subfertile because of their disease activity and not infertile, as suggested by Fielding and Cooke.

Results of the study by Homan and Thorbjarnarson (16) on 78 women with Crohn's disease who were potentially capable of bearing children agreed with the works of Fielding and DeDombal. They found the fertility rate for all patients with Crohn's disease (0.063) to be significantly lower than the national average (0.088) with $p = 0.012$. Homan and Thorbjarnarson attributed this lowered fertility rate to a combination of physical as well as psychologic factors; they also suggested that since Crohn's disease often involved the reproductive organs, the resulting periadnexal adhesions were in part responsible for the infertility. The psychologic effect of suffering from Crohn's disease, however, was also considered a cause. Many of these women suffer decreased libido from their chronic illness, as well as fearing the effect of pregnancy on the disease, or vice versa. Some are discouraged from becoming pregnant, and some elect therapeutic abortion for fear of the outcome of their pregnancy.

When considering the site of intestinal involvement, Homan's study showed only small-bowel disease to be associated with a significantly lower fertility rate. This differs from the earlier studies of Fielding et al and DeDombal's as large-bowel involvement, Crohn's colitis, or enterocolitis was not associated with a decreased fertility rate.

In two recent reviews of pregnancy and Crohn's disease (17, 18), the subject of fertility is discussed. Korelitz (17) states that women who had difficulty conceiving had evidence of an active disease state, though statistically the rate of conception fell into the range of the average population. Furthermore, despite previous suggestions regarding the importance of periadnexal adhesions, Korelitz felt that infertility was rarely due to blockage of the fallopian tubes by adhesions, but rather was due to the primary manifestations of the disease such as fever, loose stools, fistulas, and anemia.

Finally, two interesting points regarding this topic are discussed by Jarnerot (18) in his recent Scandinavian study. Those with inactive or mild disease had better chances of conception as noted by the author. In comparing medically to surgically treated women with Crohn's disease, the surgical group demonstrated a higher fertility rate. Thus, if the disease could be brought into a more permanent state of quiescence, the rate of fertility increased.

A second point raised in this report was the effect of the drugs which are frequently used in Crohn's disease on fertility. Corticoids or sulfasalazine has not been demonstrated to affect female fertility; however, spermiogenesis was affected by treatment with sulfasalazine, possibly resulting in male infertility. Several reports followed (19–21) that demonstrated this effect to be rare and reversible within 3–4 months after withdrawal of the drug.

Influence of the Disease on Pregnancy. Without evidence from careful study, many formerly believed that Crohn's disease had an unfavorable effect on pregnancy. Bearing this misconception in mind, it was often suggested to women who suffered from this disease to avoid pregnancy or to undergo abortion. Evidence has since been acquired that Crohn's disease does not have any negative effects on pregnancy, and the presence of the disease is no longer an acceptable reason for therapeutic abortion.

In the previously cited study by Crohn et al (13), it was found that of the 84 pregnancies in

53 patients with Crohn's disease, when a woman became pregnant the effect on the pregnancy was only mildly unfavorable. If the ileitis occurred first during the gravid state, however, more severe effects on the fetus were seen. In the study by Jarnerot an increased risk of stillbirths was found when Crohn's disease first developed during pregnancy.

In other contrasting reports that followed (22–24), no untoward effects were found to result from previously established Crohn's disease. Indeed, Korelitz (17) found that the incidence of premature births, spontaneous abortions, stillbirths, and congenital anomalies for patients with Crohn's disease was actually lower than that in the general population. However, in the presence of active disease, the rate of spontaneous abortions was much higher than that for the overall Crohn's population.

Eighty percent of the wanted pregnancies in Homan's series (16) resulted in live births and 17% in abortion. The latter figure is comparable with the 15% abortion rate estimated for all pregnancies in the general population (25). Two of the deliveries (6.2%) for live births were performed by cesarean section, a figure similar to the estimated incidence of cesarean section among live births in the United States (26). Only one relatively mild congenital anomaly, polydactylism, was seen.

DeDombal et al (15) found 88% of pregnancies to result in a live child. The risk of prematurity, stillbirths, abortion, or congenital abnormality was not increased in Fielding's study (22), and the abortion rate was only 13.3%. Similar conclusions were reached by Norton and Patterson (23) and Mogadam et al (24).

Pregnancy, Crohn's Disease, and the Postpartum Period. Much information has been collected regarding the course of pregnancy on Crohn's disease. Many of the studies cited here were in agreement on the outcome of this combination.

To date, the most extensively described study remains that by Crohn and his co-workers (13), which was conducted at The Mount Sinai Hospital, New York City, and reported in the literature in 1956. The 84 pregnancies in the 53 patients they studied were analyzed by groups according to the ileitis activity during the pregnancy (as established by Abramson et al (27). The patients were divided into four groups, I, II, III, and IV. In group I, those with a previous history of regional ileitis, inactive or quiescent at the time of pregnancy, it was found that 62% of pregnancies were carried to term without recurrence of the disease. Twenty-two percent had intestinal symptoms during the course of pregnancy and 16% during the early postpartum period. Furthermore, of those with previous supposedly successful surgical procedures, 81% had uneventful pregnancies. Pregnancy presented a serious problem to those without prior surgery either during the gravid state or in the postpartum period, with exacerbation of the disease process seen in many of these women.

The patients in group II had active ileitis at the time of conception. As in group I, a large percentage (87% in this case) carried to term without aggravation of the intestinal disease. The postpartum recurrences in this group were frequent and severe, appearing in 46% of the cases despite uneventful pregnancies.

Group III included patients in whom the onset of ileitis occurred during the pregnancy. Though this consisted of only three cases, the onset of ileitis during pregnancy was shown to impose a serious threat to both mother and fetus. There were no full-term pregnancies, and two ended in spontaneous miscarriage. Maternally, acute symptoms of the disease were experienced both during the pregnancy and in the postpartum period.

Finally, the patients with ileitis beginning during the postpartum period comprised the fourth group studied. Four of these six patients experienced symptoms during the immediate postpartum period, the other two within the first 3 months of delivery. If the ileitis first occurred during the gestational period, the course of pregnancy was more likely to be severe; but if ileitis was first seen in the postpartum period a mild effect was likely. Finally, those with previous successful surgery did better than patients who had undergone conservative management alone.

Other earlier reports, such as those by Norton and Patterson (23), Fielding (22), and DeDombal et al (15), demonstrated that pregnancy did not exert an adverse effect on the course of Crohn's disease, nor was an increase in mortality seen. In Norton and Patterson's work (23), it was demonstrated that there was an almost even chance of having an attack of "active disease" in a given year for pregnant (40%) and nonpregnant (43%) patients with Crohn's disease.

Fielding (22), in fact, reported some improvement in the symptoms and signs of Crohn's disease during the pregnant period, and most women went on to normal full-term deliveries. Many exacerbations of the disease were seen during the postpartum period. Fielding reported that one fourth to two fifths of patients went on to experience exacerbations after delivery. DeDombal et al (15) showed an overall 40% relapse rate, of which 60% occurred in those on conservative management alone.

Reports by others also demonstrated that pregnancy did not exert an adverse effect on Crohn's disease, but at termination of the pregnancy, some relapses were shown. In Homan's (16) series of 42 patients, 90% did not experience any exacerbation of the disease while pregnant. In the postpartum period, 24% did have relapses, which he attributed to hormonal changes. There was no evidence that any particular patient or group was more likely to develop symptoms after delivery.

The 90% rate quoted in Homan's study (16) was the highest asymptomatic group reported. Others found that quiescence or worsening of disease during pregnancy correlated with its activity at the time of conception. The figures reported from the Scandinavian study by Jarnerot (18) showed that of those with inactive disease at the onset of pregnancy, 74% remained quiescent and 26% became worse. In the group with active disease, 35% became better, 12.5% became worse, and 52.5% remained unchanged. The puerperium marked a period of increased risk of flareup in both groups.

Korelitz (17) stated that if Crohn's disease is active before pregnancy, it is likely to remain active or get worse. This was likely to occur in the third trimester. Furthermore, prognosis of subsequent gestations was not related to previous pregnancies, but to the nonpregnant state each time.

Mogadam et al (24), in a national survey, reviewed the course of 146 pregnancies in women with Crohn's disease. There was evidence that the course of disease was significantly milder in patients who became pregnant while in remission as compared to those with mild to severe disease ($p < 0.0001$). Sixty-five percent of those with active Crohn's disease before pregnancy continued to have active disease, whereas 78% with quiescent to mild disease had no exacerbations. These findings of remissions and exacerbations did not correlate with maternal cortisol activity, unlike those previously reported by DeDombal et al (15), who suggested that the rise in serum cortisol during late pregnancy accounted for the remissions seen, whereas the fall in this concentration postpartum was responsible for the relapses seen in inflammatory bowel disease. Mogadam et al went on to state that the elevated plasma free cortisol in pregnancy was not excessive, but was in fact needed to balance the competitive inhibition of the glucocorticoids to tissue receptors as a result of the elevations in the plasma progesterone levels.

Drug Therapy in Pregnancy. Sulfasalazine, ACTH, adrenal steroids, and immunosuppressives (such as 6-mercaptopurine and azathioprine) are all drugs that are commonly used in the management of inflammatory bowel disease. The effect of these drugs, with particular emphasis on fetal development, has recently been reviewed in the literature by various authors. Studies on animal species have demonstrated that cleft palate and stillborn fetuses may result when large doses of cortisone are used during pregnancy. Although this subject still remains controversial, it is thought that these drugs are reasonably safe when used during human pregnancies (28).

Small molecules with molecular weights less than 1000 and nonionized drugs such as alcohol, salicylates, sulfonamides, and corticosteroids are easily transported across the placenta (29). They cross from the maternal to fetal circulation by simple diffusion.

Sulfasalazine, a drug widely used in the management of inflammatory bowel disease, is formed by a diazo bond that links a salicylate radical to sulfapyridine (SP). It reaches the colon virtually intact after oral ingestion, where it is split by bacteria into SP and 5-aminosalicylic acid (5-ASA). Although the ASA moiety is the active part of the molecule, it is the former, the SP component, which is responsible for almost all the complications of sulfasalazine therapy.

In a study by Azud Kahn and Truelove (30) of five patients with ulcerative colitis who became pregnant while on maintenance treatment with sulfasalazine, it was demonstrated that this drug crossed the placenta. The mean concentration in the cord serum was found to be half that of the maternal serum. The total-SP concentration in the cord, however, was identical to that of the maternal serum. The free-SP value was significantly lower and the acetylated-SP value significantly higher than maternal values. No unfavorable effects on the pregnancy or on the fetus were demonstrated. Nonetheless, the authors stated that a theoretical risk of fetal complications as a result of treatment exists, taking into consideration the concentration of metabolites that reach the fetal circulation.

Azud Kahn and Truelove also studied the effects of the concentration of sulfasalazine therapy on breast-feeding patients. They found that both sulfasalazine and SP passed into breast milk. The mammary transfer of the former was about 30% that of the maternal serum, and the total-SP concentration was about 50%. They concluded that since the concentration of this drug and its metabolites was much lower in the breast milk as compared to maternal serum, it is unlikely that harmful side effects exist.

One of the largest studies dealing with inflammatory bowel disease and drug therapy during pregnancy was that undertaken by Mogadam et al (31). They reviewed the course of 531 pregnancies occurring in women with ulcerative colitis and Crohn's disease. Of this total number of patients, 244 patients (137 with ulcerative colitis and 107 with Crohn's) did not receive either corticosteroids or sulfasalazine, whereas 287 (172 with ulcerative colitis and 115 with Crohn's disease) had taken either or both of these during the course of the pregnancy. From the results obtained, they found that the frequency of fetal complications was significantly lower in both the treated and untreated groups as compared with the reported rate in the general population. After studying each group individually, the authors concluded that the use of these drugs in pregnancy associated with ulcerative colitis was unlikely to cause an increase in fetal morbidity or mortality. More complications were seen in the treated group of Crohn's patients with severe disease than in the untreated group, but this rate was still less than that of the general population. In addition, the higher complication rate seemed to be associated with disease-related factors rather than the use of these drugs. Finally, the authors concluded that either or both of these drugs may be used in the management of inflammatory bowel disease during pregnancy as in the nonpregnant state.

In light of the evidence presented earlier in this article, i.e., that the outcome of the pregnancy was related to the activity of the disease state, it seems reasonable that every effort must be made to alleviate the course during pregnancy. This management may require therapy with the drugs mentioned above. Based on the data collected thus far, the benefits far outweigh the risks of potential complications with these medications, and the physician should not withhold this treatment because of pregnancy.

Surgery During Pregnancy. The course of inflammatory bowel disease may worsen during pregnancy. The indications for surgical intervention during the gravid state are the same as in the nonpregnant patient. These include perforation, bleeding, obstruction, and toxic megacolon.

Reports in the literature dealing with bowel surgery during pregnancy have described a high fetal and maternal mortality (14, 32, 33). In a recent editorial (22), Fielding states that every effort should be made to avoid surgery in pregnancy and to treat the inflammatory bowel disease with medical management. However, although the likelihood of fetal survival is decreased because of surgery, the outcome is far worse if surgery is not performed for fulminating disease unresponsive to medical management alone (14).

Once the decision to operate on the patient is made, the question of which surgical procedure to perform arises. Regional enteritis is best handled by a small resection with primary anastomosis. This site presents fewer problems than operative management of large-bowel disease. In the latter case, terminal ileostomy with colectomy and turn-in of the rectal stump or proctocolectomy is the procedure of choice (34). Bypass ileostomies and various drainage procedures should be avoided since they are usually followed by a stormy postoperative course and in more than two thirds of the reported cases result in a stillborn fetus and a maternal death.

Conclusion

Many issues arise in regard to the management and prognosis of inflammatory bowel disease during pregnancy. The results of various studies on pregnancy and Crohn's disease have been reviewed and commented upon in this paper. The application of this knowledge is critical in dealing with this unique situation, for it is only with awareness of this information that the best treatment plan for each patient can be designed and the healthiest outcome of pregnancy achieved.

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VOLUME 52 NUMBER 6 JUNE 1985

Combination Cancer Chemotherapy

Samuel Waxman, M.D., Guest Editor

A Symposium in Honor of Ezra M. Greenspan

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Volume 52
Number 6
June 1985

CONTENTS

Medical Manpower and Other Strategic Issues *James F. Glenn, M.D.* 405

Private-Sector Health-Care Initiatives *Samuel Davis, M.S.* 409

Mount Sinai Journal Awards 414

COMBINATION CANCER CHEMOTHERAPY
A Symposium in Honor of Ezra M. Greenspan

Introduction *James F. Holland, M.D., and Samuel Waxman, M.D.* 417

Preclinical Chemotherapy: Historical Aspects *Abraham Goldin, Ph.D., M.Dhc.* 419

Cancer Chemotherapy: Past Is Prologue *Daniel S. Martin, M.D.* 426

Multiple Primary Neoplasms and Tumor Diathesis *Howard R. Bierman, M.D.* 435

Combination Chemotherapy of Breast Cancer *Richard G. Cooper, M.D.* 443

High-Dose Combination Chemotherapy: Why, How, and When *Lucien Israël, M.D.* 447

Safer Combination Chemotherapy Using a Kinetically Based Experimental Approach *Leonard A. Price, M.D., MRCP, and Bridget T. Hill, Ph.D., FRSC, FIBiol* 452

Current Status and New Vistas in Combination Chemotherapy *Emil Frei III, M.D.* 460

Prior Tuberculosis in Long-Term Survivors of Breast and Ovarian Cancer from a New York Oncology Practice (1954–1974) *Ezra M. Greenspan, M.D.* 465

continued

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CONTENTS *continued*

GENERAL ARTICLES

Colorectal Cancer (Duke's Group B2, C1, C2): Adjuvant Chemotherapy and Toxicity *Umberto Caruso, M.D., Marco Elli, M.D., E. Cravotto, M.D., Giuseppe Tisone, M.D., P. A. Lombardo, M.D., M. Silvaroli, M.D., C. Ficorella, M.D., E. Cortesi, M.D., and Carlo U. Casciani, M.D.* 470

Solitary Neurofibroma of the Gallbladder: Report of Three Cases and Literature Review *B. Ilie, M.D., and A. J. Behar, M.D.* 473

SPECIALTY NOTES

ENVIRONMENTAL MEDICINE *Alf Fischbein, M.D., editor*

New Dimensions in Occupational Medicine *Alf Fischbein, M.D.* 478

Modified Nucleosides and Early Detection of Occupational Cancer: A Challenge for the Future *Alf Fischbein, M.D., Opendra K. Sharma, Ph.D., and Ernest Borek, Ph.D., M.D. (Hon. C.)* 480

GASTROENTEROLOGY *David B. Sachar, M.D., editor*

New Drugs in Gastroenterology *Gerald Friedman, M.D., Ph.D.* 484

NEUROLOGY *L. Jay Turkewitz, M.D., editor*

Current Therapy of Demyelinating Neuropathies *Marvin I. Ruderman, M.D., and L. Jay Turkewitz, M.D.* 490

SURGICAL PATHOLOGY *Ira S. Schwartz, M.D., editor*

Malignant Histiocytosis *Ronley Plous, M.D.* 496

The Mount Sinai Journal of Medicine
Vol. 52, No. 6, June 1985
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Medical Manpower and Other Strategic Issues

James F. Glenn, M.D.

Medical manpower is one of the most important concerns facing the health care industry. Decisions made now regarding training needs and strategies will have a profound impact on the total health-care cost picture for years to come. This is particularly significant when we consider that health care is the second largest industry in the nation, exceeded only by government in total expenditures.

In recent decades we have seen a dramatic increase in numbers of physicians. Due to the looming spectre of malpractice suits, many physicians are practicing defensive medicine, which raises costs. We can boast of a dazzling array of achievements in research and technology, but they also increase the cost of medical care. At the same time, we face mounting pressure for cost containment from virtually every sector of society.

It is simply not possible to satisfy the conflicting desires of maximum care and minimum cost. There is no free lunch. Instead, we must carry on a continuing dialogue with legislators and the public that aims to keep the conflict in balance.

For some time, the cost of medical care has been the whipping boy of politicians and the general public. We are castigated for rapidly rising costs despite the tremendous achievements we have realized. In this country we have the most advanced medical technology in the world; we have prolonged human life almost to its biological limit; and we are enjoying better health than in any other nation and at any other time in history. Nonetheless, politicians continue to attack "skyrocketing" health-care costs. (The increase in the cost of government is roughly a hundred times as great as the increase in health-care costs since World War II.)

We should be particularly concerned about the Reagan administration's recent efforts to cut federal expenditures for medical research. Should this occur on a significant scale, advances in medicine could be paralyzed. Communist China provides an excellent example of the ultimate result of such actions. For thirty years, medical research in that country languished in an impoverished environment; the doors to any sort of academic inquiry were closed. Only now is China making a feeble effort to recapture the scientific progress it might have made during this period of intellectual repression.

For us to pursue such a path in this country would be a foolish economy. This is not to deny, however, the pressing need to address the issue of controlling costs in medicine. Any realistic attempt to do so must focus specifically on the manpower question. There are numerous data to support the argument for constraint in this area by the medical education enterprise.

Interrelationship of Major Issues

Many of the major issues in health care are interrelated, and all of them have an impact on decision-making regarding medical manpower. In no particular order of importance, they include:

Medical care costs: At the end of World War II, health care expenditures were 4% of the gross national product (GNP). Given current trends, by the turn of the century health-care expenditures will account for more than 20% of the GNP. Is this reasonable or affordable?

Based on a lecture delivered February 21, 1985 in a seminar series, "The Health Care Environment in the late 1980s," sponsored by the Department of Health Care Management, Mount Sinai School of Medicine (CUNY).

The author is president, The Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029. Address reprint requests to the author there.

Mode of medical care delivery: Has the traditional model of hospital care become outmoded? Are other mechanisms needed? We must consider greater use of ambulatory care, day-stay beds, and other methods to address health care needs in the future.

Cost of medical education: The delivery of medical care is dependent upon undergraduate and graduate medical education, which is therefore a national resource. How, and to what extent, should such education be funded?

Care of our growing geriatric population: The elderly are the fastest growing population in this country. They represent a mounting problem in health-care delivery.

Humanism in medicine: The art of medicine is just as important as the science. Are today's medical students being properly prepared in this important area?

Surplus of medical manpower: This problem is intimately related to the question of medical education and is dealt with at some length below.

Fraud in medical licensure and research: This is a disappointing and frightening byproduct of the highly competitive nature of medicine in the 1980s.

Quality controls in medical practice: How do we measure the product that is being delivered? It is difficult to monitor quality, because the doctor–patient relationship is a highly personal and confidential one.

Health in Third World nations: This remains a major problem that has not yet been addressed effectively. We have shared the medical expertise of the United States and other developed countries in only a token fashion with the Third World.

Recurring medical malpractice crises: This issue has surfaced periodically since 1970. In New York State, the most recently mandated increases in medical malpractice insurance premiums will serve to push the cost of health care even higher.

Physician Availability and Health-Care Costs

There is no doubt that physician availability is a major factor in the cost of medical care. The average patient cannot be expected to know what is needed in terms of medical care, attention, and technology. Thus, the patient will use the resources that are available. It is ultimately the physician who bears the decision-making responsibility for how the health-care dollar is spent.

Clearly, the more available we make medical care to the general public and the cheaper it becomes, especially if it is perceived as "free," the greater the potential for overutilization of these resources.

This question has never been adequately addressed; it is not a popular topic. But we must now confront the problem. It is my opinion that an increased number of physicians inevitably leads to increased utilization of medical technology and medical resources, and a resulting increase in cost to society. It is incorrect to assume that the way to bring down the cost of medical care is to have a physician available to everyone at all times. On the contrary, we must devise a system that uses the best available resources with some yardstick for judgment as to their distribution.

How is this to be accomplished? There is no magical answer; rather, a number of different approaches may result in bringing the situation into better balance.

Many leaders in academic medicine today agree on the necessity for some form of modulation of medical education, in terms of both number of schools and number of students. We can further agree that needs for specialists should be carefully monitored, preferably by the professional community, to avoid overproduction of one specialty while another is woefully neglected. Geographic distribution of specialists must also be monitored and made more rational in terms of meeting health-care needs nationally.

It is also essential that we adhere to the development scheme of a three-tier medical system for delivering primary, secondary, and tertiary care. We must regionalize health care by developing a network of hospitals that work together cooperatively rather than competitively. This major problem defies simple solutions, but overcoming it is crucial to cost containment.

We must also continue and increase our efforts to make the public aware of health-care costs. A better understanding by consumers is one of the contributing factors in the current downtrend in hospital occupancy. Hospitals around the country are showing a reduction in patient days of approximately 10%, which can be explained in large part by greater consumer awareness of cost.

Finally, and perhaps most difficult, we must train physicians for a complex role. We have become so scientifically oriented that we often fail to recognize that physicians can and should be leaders in their community. We must prepare today's medical students to speak out on health policy and other issues as well as to provide clinical care and involve themselves in research.

Physician Oversupply: The Underlying Factors. A brief review of the numbers of first-year medical students provides an explanation of the current oversupply of physicians. Throughout the 1930s and 1940s and into the 1950s, between 5,000 and 7,000 students entered medical school annually. About 1960, these numbers suddenly accelerated upward as a consequence of government intervention.

In 1960, there was a general perception that the nation faced an undersupply of physicians and that the system should be force-fed. Capitation grants were instituted by the federal government at that time. Medical schools were told that if enrollment was increased by 20%, a grant of $5,000 per student per year would be awarded for every student in the school. If enrollment was not increased by 20%, no additional funds would be awarded.

The response was entirely predictable. Every medical school in the country increased its enrollment. By 1970 the number of new students in medical schools was 10,000; by 1975, 15,000; and by 1980, about 17,000. Furthermore, additional bonuses and rewards were created for establishing new medical schools. Medical schools rapidly increased in number, from 80 to 127 at the present time.

This trend has now begun to flatten, and medical school enrollments have gone down slightly in the last two years. However, we have more than tripled our capacity to produce physicians since the beginning of World War II and are presently turning out more physicians than we need in nearly every specialty group. The Graduate Medical Education National Advisory Committee (GMENAC) study in 1980 indicated that shortages of physicians still exist only in rehabilitation medicine, emergency medicine, and adult and child psychiatry.

Cutting the Number of Medical Schools. Today there is absolutely no rational justification for creating a new medical school in this country. In fact, to make any meaningful reduction in the cost of medical education, we should be cutting the number of schools rather than the number of students. For example, reducing the student body at Mount Sinai School of Medicine by 10% would have little appreciable effect on the medical school's overall cost of operation, though it would have some beneficial effect for society in reducing the excess number of physicians. The school itself would continue to require the same physical plant and the same staff, achieving no savings.

True cost effectiveness requires reducing the number of medical schools in whatever amount is deemed necessary to bring the number of physicians produced in balance with our national need for manpower. While there may be disagreement as to what the number may be, there is no disagreement that we are presently in a mode of overproduction.

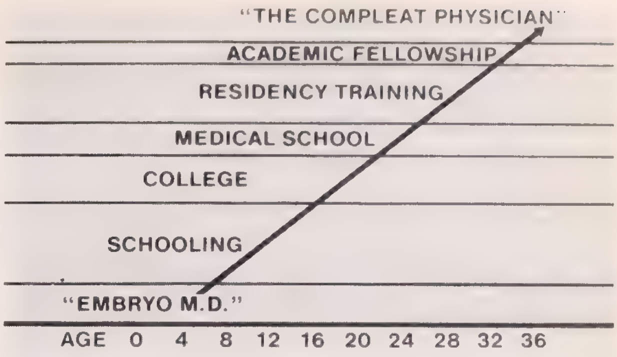
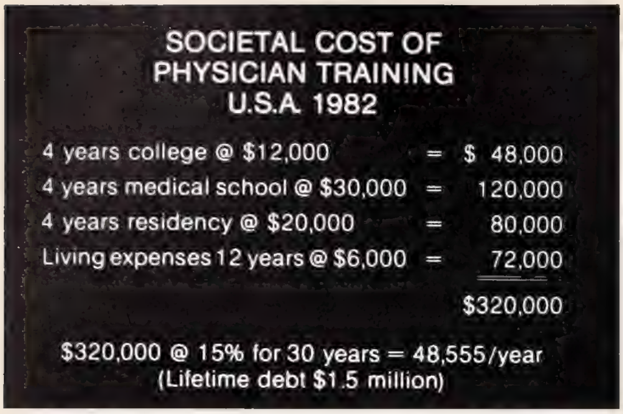


Fig. 1. The making of a physician.

Government has already taken some steps to turn this situation around. In 1981 and 1982, capitation grants to medical schools were eliminated in two decrements. Certain types of support for graduate medical education have also been reduced, restricted, or completely discontinued, including many fellowship and medical training programs which at one time were the backbone of most academic medical centers.

Need for Long-Range Plans. However, the solution to the problem of oversupply is not as simple as turning a faucet on and off. Medical education is a long-range process. The average physician enters practice at age 30, and his or her prior course has been a protracted one. The decision to consider medicine as a career may first have been made in high school; by college the student becomes well focused toward a medical education; this is followed by four years of medical school and at least three years of residency training. Any thought of attempting to modulate the supply of physicians year by year is therefore preposterous. The true time lag is on the order of ten years; if we wish to affect the supply of physicians in 1995, we must begin now (Fig. 1).

It is unlikely that a public consensus can be achieved on the number of physicians that will be needed in ten years. The medical community itself must take the responsibility for making such a projection and carrying it out. I am reassured and gratified that New York State is addressing this question through its Commission on Graduate Medical Education and several other modalities. These efforts will help to create a rational basis for decision-making on the number of physicians needed, and consequently the number of medical schools, medical students, and residents required to meet this need.



SOCIETAL COST OF
PHYSICIAN TRAINING
U.S.A. 1982

4 years college @ $12,000 = $ 48,000
4 years medical school @ $30,000 = 120,000
4 years residency @ $20,000 = 80,000
Living expenses 12 years @ $6,000 = 72,000
$320,000

$320,000 @ 15% for 30 years = 48,555/year
(Lifetime debt $1.5 million)

Fig. 2. Societal cost of training a physician in the United States in 1982.

Social Costs of Physician's Training. Costs must be taken into account when such decisions are made. I estimate the total societal cost of producing one physician to be on the order of $320,000. This figure does not include what the individual pays for medical education; at Mount Sinai our tuition is now $13,000 a year, and we are not among the most expensive schools. The societal cost is borne by the community at large, either through their tax payments or their philanthropic contributions (Fig. 2).

The $320,000 total is based on an estimated $12,000 annually as the societal cost of a college education. In medical school, the annual cost to society is approximately $30,000. This is derived from our 1983 estimate at Mount Sinai of a total cost of $42,000 per student per year. We calculate the annual societal cost during the years of residency to be $20,000. Living expenses during the twelve years of college, medical school, and residency are calculated at a rate of $6,000 annually.

If the $320,000 cost to produce one doctor were amortised over a 30-year period of active practice at 15%, the annual debt would amount to nearly $50,000, for a lifetime cost of $1.5 million. These figures bring the underlying question into sharp focus: to what degree can society afford to add doctors to the community at this staggering cost?

Some medical schools are already taking action to reduce enrollment. Duke University School of Medicine has cut back its student body by 10%. New York University School of Medicine has reduced enrollment, by 5% last year and another 5% this year. But even if some other schools follow suit, the magnitude of the problem is such that more significant actions than this are required to solve it.

Conclusion

Controlling physician manpower is a key factor in controlling the overall cost of health care. Reducing enrollment in medical schools is an important but insufficient step in terms of manpower needs and strategies with relation to cost containment. Serious thought must also be given to closing entire schools. In addition, more vigorous efforts must be made to devise alternate methods of health-care delivery. We must increasingly turn to ambulatory care rather than hospital stays, and to nurse practitioners, physician assistants, and other paramedical professionals to take over much of the responsibility for routine medical care. This will require adjustment not only within the medical community; it also calls for a major public education effort to convince patients that many of their needs can be met by members of the health-care team who are not physicians.

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Private-Sector Health-Care Initiatives

SAMUEL DAVIS, M.S.

The Flexner report at the turn of the century marks the beginning of the real change in modern medicine, health care, and medical education; the time when medical schools developed organized curricula, and when teaching programs began to take hold at what were to become teaching hospitals.

At that time, funding for education and medical care came from three primary sources: from the public in the form of support for public medical schools and hospitals; from philanthropy for voluntary institutions; and from payments in the form of patient fees or tuition payments for students.

The system went comfortably on that basis until conditions began to change in the 30s, when people began to find it difficult to pay their medical bills. We saw the development then of hospital insurance, medical insurance, indemnity insurance, and the birth of Blue Cross as a third-party intermediate between patient and hospital and employer and employee.

By the end of World War II, we saw an explosion in medical information and technology, and the beginning movement of dollars from the public sector into programs of the voluntary sector. One example: the decision of New York City not to build any more municipal hospitals, but rather to contract with voluntary hospitals for ambulance, clinic, and ward service, and to pay a set fee per ambulance call, per visit, or per diem.

Philosophy: Health Care Is a Right

Gradually, there developed in our country a philosophy that health care is a right, and that the newly developing science and technology in health care should be available to all people. We began to see some dramatic changes in the provision of broad-based government funding, to the voluntary sector and the public sector. There were investor-owned institutions, not affiliated with each other, but freestanding, individual institutions, largely physician-owned.

The velocity of the health-care-as-a-right concept, plus the application of the new technologies, took expression in such forms as the Hill-Burton Act for construction of voluntary hospitals and culminated in a quantum leap in health-care financing history. We saw the arguments over national health insurance, the attempt to pass the Forand Act in the Truman administration, the efforts of the two Wilburs—Mills and Cohen—in the successful development of Medicare. We saw passage of Medicaid as the expression of the government's obligation to poor people for public funding of both a public system and a voluntary system.

The 60s were a great time for a hospital administrator—money for operations and construction and equipment were easy to come by. The source of capital for the health-care field was largely public and private, with philanthropy occupying an ever smaller percentage of the total, as the years went on. Then came the energy shortage of the 70s, the Report of the Club of Rome, which described limits to growth. And, in our own country, the recognition that the government could not do everything, that the prevailing social philosophy could not meet all of the society's needs, and that sooner or later, social programs would have to be cut.

And, of course, in New York, we saw operating revenues chosen as the mechanism for the control

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Based on a lecture delivered January 17, 1985 in a seminar series, "The Health-Care Environment in the Late 1980s," sponsored by the Department of Health Care Management, Mount Sinai School of Medicine (CUNY).

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of health-care costs, the same pattern now being followed throughout the rest of the country.

Today, we are seeing other ways of capital expenditure control in New York, through the combination of Health Systems Agency programs, State Hospital Review and Planning Council programs, and Office of Health Systems Management programs. But the capital needs that exist both in the state and the United States are greater than the public or the voluntary sector can meet.

Therefore, in effect, there is a major national issue of the formation of capital. I believe it is a dialectical argument which drives the very dramatic changes we are seeing in the health-care field today. *He (or she) who owns and controls the factors of production will ultimately influence, if not control, production.* That's the underlying thesis, which in the case of health care seems to be pragmatically working on the positive side, in the context of our total social and economic structure.

Troubles and the Tilt To Private Initiative

Trouble breeds change. The hospital medical supply companies are in trouble. Independent freestanding voluntary hospitals are in trouble. The physician in independent practice—and indeed the independence of physicians—is in trouble. Teaching hospitals are in trouble. There is increased polarization in this country between voluntary and for-profit hospitals, and between teaching and community hospitals. There is a widening gap between hospitals and physicians.

Hospital supply companies are cutting employee benefits. American Hospital Supply, which has a huge joint venture in the works, laid off 300 workers in December, and has recently gone to a centralized form of controlled management from a long history of decentralized control. During the last week in February, Hoffman-La Roche laid off 12% of its American payroll, 1,000 workers. Other companies are cutting back, merging, diversifying.

Medicare and Medicaid are under federal budget pressures. The Reagan administration in fiscal 1986 cut Medicare 3.7% from fiscal 1985, with a predicted $19-billion cut in Medicare for the next three years. A piece of legislation proposed by Senator Durenberger of Minnesota requires that medical education should be pulled out of Medicare reimbursement and that the states should administer block grants for postgraduate medical education.

Uncertainty in Medicare

Uncertainty about the future of Medicare has propelled healthy not-for-profit teaching hospitals into selling out to investor-owned chains. The Wesley Medical Center, in Wichita, Kansas, is in the process of being sold to the Hospital Corporation of America for $265 million. (As the Wesley Medical Center president, also named Davis, said, "Free enterprise works in the health care field.")

Other teaching hospitals are also lining up for private support. George Washington Hospital, Washington, D.C., is close to a decision on whether it will sell or lease to American Medical International. St. Joseph Hospital, Omaha, Nebraska, one of the nation's largest Catholic teaching hospitals, has been sold to AMI. In Louisville, Kentucky, of course, Humana manages the university hospital. The Hospital Corporation of America Vanderbilt Hospital in Nashville, Tennessee, builds and operates a new 88-bed children's and adolescent hospital, and Kansas City, Missouri, does a joint $8-million 100-bed psychiatric hospital deal with Research Health Services. And on, and on, and on.

Other Pressures Favoring Private Initiatives

In the first six months of 1984, 60,000 fewer employees were working in hospitals than in 1983 on an annualized rate. We've seen a 3% decline in the number of people employed by hospitals. Utilization has decreased 5%. Admissions are declining, even in New York.

The major for-profit chains show an earnings boost. If the proposed flat tax is passed in any form, it will favor the investor-owned and disfavor the voluntary institutions. Voluntary institutions today are having difficulty getting tax-exempt financing for capital expenditures.

FHA is getting tougher and tougher in granting its insurance. State regulatory bodies are becoming more and more difficult in granting certificates of need, the first step in tax-exempt financing. Despite the pent-up need in this country, financing of these institutions is not going to get easier.

If the flat tax is passed, the for-profit institutions will have an easier time generating capital than the voluntary institutions—the voluntaries will find that the flat-tax legislation will put a crimp in their all-important philanthropic sources.

Access to Capital: The Core of the Need

The key issue in this dynamic period is access to capital; HCA, as the leading investor-owned chain, is changing, becoming more and more of a total health-care company, even adding an insurance company. Investment bankers indicate in their national studies that $200 billion is needed between now and 1990 for hospital plant replacement, renovations, and modernization. Thirteen billion is needed in New York State alone.

The Health Care Financial Management Association estimates that the average hospital in the United States has only 37% of its replacement needs funded. A major issue—how capital will be reimbursed under Medicare—will soon be before the Congress. The proposal which seems to have the most currency today is an add-on to the Medicare Diagnosis-Related Group rates at the end of 1985 in the amount of 7%. Those of you who understand the finances of this institution and others like it know how impossible it will be for this type of teaching hospital to live with 7% to meet its capital needs.

Human Capital Is Also a Factor

Human capital is also involved in the equation. I think there are major problems in the governance of voluntary institutions. The multihospital voluntary organization has diminished the role of individual trustees. In addition, it gives them all the same problems as for-profit directors: product liability, Social Security liability, medical staff appointment liability, and the rest—without any of the benefits accruing to for-profit directors.

Dr. Robert Heyssel, president of the Johns Hopkins Hospital, has told the Association of American Medical Colleges about his concerns about business being resistant to paying teaching hospitals a premium, and registered his reaction to the pressure now going on in government to take out the cost of teaching in reimbursement to teaching hospitals—thus putting the teaching hospital and the community hospital into competition on an equal dollar-to-dollar basis, for the delivery of a very different product or products.

A prediction: I think ultimately we're going to see the segregation of the cost of teaching from the cost of patient care. That does not bode well for educational programs.

I also think that ultimately we're going to see the division and segregating out of the cost of research from the cost of patient care.

I think there are some real problems in hospital governance in the not-for-profit hospitals, in addition to the problem of the exposure of trustees to liabilities. In voluntary hospitals, we have seen a heavy emphasis on operations and an insufficient emphasis on strategy. We have seen the goodwill effort of trustees as they have tried to address the simultaneous satisfaction of competing constituencies within these hospitals. We have seen great opportunities lost while trustees dealt with compelling policy questions in their time-consuming and awkward decision-making process. If the voluntary hospitals are to compete, they're going to have to change, and change quickly.

Blue Cross, which for years has acted as a fiduciary—business pays Blue Cross, Blue Cross pays the hospital—has suddenly begun to make moves away from that pattern. In Cleveland, they have attempted to force cost-shopping with a reimbursement plan requiring bids for Blue Cross contracts. Only 25 of the 34 competing nonprofit hospitals were awarded contracts. Starting March 1, winners will be reimbursed 100% for treating Blue Cross members, losers only 70%. In this dynamic, somewhat crazy environment, we can see a couple of portents for voluntary hospitals.

They will have to move from freestanding independence and define their own future in interdependence, and through the Voluntary Hospitals of America.

Paul Starr, author of the Pulitzer-Prize-winning *Social Transformation of American Medicine,* in a 1984 seminar here at Mount Sinai New York made the point that the physician is no longer the last bastion of independent professionalism. This change is being driven by the surplus of physicians, by government efforts to contain costs, and by the rise of corporate enterprise in health. He also points out that the public investment in training health-care professionals and developing capital is declining. Which leads me away from hospitals for a bit, and into education, in which I have a personal interest.

New Forces for Change in Education

The recent report from the AAMC, "General Professional Education of the Physician" (GPEP), throws down the gauntlet to the private sector on the matter of continuing education. The report indicates that lifelong learning, adaptation of medical practice to new knowledge and new techniques, will be even more important in the future:

"The continuing education of physicians will have to be redirected towards systems and programs commensurate with the needs of physicians whose education has prepared them to be independent, lifelong learners." No one force, no individual, no one organization exists in the United States for driving change in continuing education. And unless or until there is a facility which enables that change, continuing education is going to be fragmented.

The AAMC talks only of physicians, naturally. The same mandate is no less applicable to nurses, dentists, hospital administrators, pharmacists, and other allied health-care professionals.

Which allows me to introduce the subject of EcuMed, the focus of my present activities. It is another case of private capital taking the lead, introducing a new learning environment for health-care professionals, in which it can ultimately become that major force in continuing education described in the AAMC report.

Other New Directions

Another illustration of changes taking place is the rapid move of for-profit organizations into medical research. We have seen Hoechst-Roussel Pharmaceuticals supporting basic research at Massachusetts General Hospital. And the most telling examples of the movement into clinical research are the cases of Mr. Schroeder and Mr. Haydon and the whole artificial heart program at the Humana Hospital. I think this trend will grow.

When one examines the Administration's plans for the NIH, they are looking for an 8% cut this year, and deeper ones in future years, seeking a level of support for no more than 5,000 major grants. That's shrinkage of public capital.

Shrinkage of private capital is also apparent, not because there is less of it, but because there is more demand for roughly the same amount. This creates a vacuum into which private capital, drawn from the marketplace in its own self-interest, will have to move.

Voluntary Hospitals of America (VHA) embody the kind of realism and knowledgeable strategy I've been talking about. With 400 hospitals and more coming, VHA have a purchasing budget of $3 billion a year, and are developing significant economic power. Their purpose, of course, is to generate enough capital and leverage to preserve the voluntary tradition in health care, but with less "voluntariness" and less governance than in the tradition we have known.

Another development to watch is whether Sears will really enter the health-care field; that would be the ultimate in one-step shopping. Sears made a huge commitment to exploring new ground, but they have yet to say whether they will stay in or pull out.

Some Conclusions

I have inventoried many of the troubles in health care: troubles in delivery, in governance, in research, troubles for educators and institutions that educate, troubles on the vendor side.

All of these troubles can be solved with money. But there are limits to growth, on the philanthropic side to be sure, and most certainly on the government side.

Given the amount of need, and the limits, private capital is the only major source changing the system downstream to meet needs to support delivery and education.

Some predictions:

I believe that voluntary institutions will continue to combine, pulling together into multihospital organizations. I believe that, like for-profit organizations, voluntary organizations will continue the trend toward vertical integration. I think that hospital admissions and patient days will continue to decline, and that hospitals will have to replace those lost revenues. They will replace those lost revenues by becoming a part of the whole vertically integrated system.

I feel that hospitals will continue to tie more closely to their physicians. I think that investor-owned institutions will do a better job of developing commercial ties with physicians.

I am convinced that voluntaries will survive, and I do not believe the ratios between voluntary and investor-owned institutions will change significantly. We may see more investor-owned hospitals in management contracts with the voluntaries, but the ownership ratio won't change dramatically.

What will change is the number of freestanding voluntary organizations, as these institutions become restructured vertically.

I think that we will see the growth of group medical practices. As Harry Schwartz has said recently in the *Wall Street Journal*, "as the pie shrinks, the inequities between various specialties begins to be apparent, and feelings and attitudes are exacerbated." Group practice is one way of addressing that problem with a more equitable sharing of income between players.

Then there's the matter of control. I think that more of the control of health care will shift away from both hospitals and physicians and toward the direction of capital. Capital will no longer be coming principally from government or philanthropy, but instead from a for-profit source which is market-oriented. I think those sources are going to exert more influence on a market-economy approach to health care.

Summing up, I've tried to review the history of hospitals, health care, and medical education according to their sources of funding since Flexner, the changes in public policy, and how public policy has adjusted public funds—and to a lesser degree, philanthropic funds in educational institutions, and health-care delivery funds.

Our world today is very different from that of the post-Flexner period, or even from the period after World War II. We find ourselves in a world where a really remarkable range of information and technology is available for application both to health-care delivery and to medical education. We must find ways of applying these new developments to health-care education, to medical education, and particularly to postgraduate education as highlighted in the GPEP report.

The opportunities are challenging. We are seeing some of them being addressed in health-care delivery. We don't see much yet in education, although I predict—in my own self-interest, I admit—that we'll see more of it, supported by the private sector.

I think the remainder of this decade will be filled with sound and fury and trouble. It is a kind of antithesis stage. We'll not see things coming together logically in a synthesis for several more years. But it will happen, and what will drive that synthesis is the formation of capital.

THE MOUNT SINAI JOURNAL OF MEDICINE AWARDS 1984/85

The Mount Sinai Journal Award

William Lewis, MD

William Lewis, MD, is the recipient of the 1984/85 Mount Sinai Journal Award for the best research or experimental paper published in the *Journal* in the award year for his paper "Anthracycline Antibiotics as Cellular Disruptors: Insights into Anthracycline-Induced Cardiomyopathy" (vol. 51, no. 3). His coauthors were Sarah E. Amelar, BA, and Saul Puszkin, Ph.D. Dr. Lewis, now an assistant professor of pathology, UCLA School of Medicine, Westwood, CA, wrote the paper as a resident at The Mount Sinai Hospital working under Dr. Puszkin.

Student Prize

Rosemaria Gennuso, MD

The 1984/85 Student Prize has been awarded to Rosemaria Gennuso, MD, for "Crohn's Disease and Pregnancy: A Literature Study" (vol. 52, no. 5), written when the author was a third-year student at Mount Sinai School of Medicine (CUNY). The author was in the City College Biomedical Education program and is now completing her residency in general surgery at the Veterans Administration Hospital, Bronx, NY. In July she begins a 6-year neurosurgery residency at Mount Sinai NY. She has a special interest in pediatric neurosurgery. The Student Prize, established in 1971, is awarded to encourage students—the group from which future leaders of medicine will come—to explore the publication process.

Globus Award

Matthew J. Kuhn, MD

Daniel J. Wallace, MD, FACP

The 1984/85 Globus Award for the best clinical paper published in *The Mount Sinai Journal* during the academic year went to two winners: Daniel J. Wallace, MD, FACP, for his paper "Fibromyalgia: Unusual Historical Aspects and New Pathogenic Insights" (vol. 51, no. 2), and Matthew J. Kuhn, MD, for "Idiopathic Pulmonary Hemosiderosis: The Importance of a Chest Radiograph in Children with Unexplained Anemia" (vol. 52, no. 5). Dr. Wallace, a diplomate of the American Board of Internal Medicine and Rheumatology, is an attending physician in the Division of Rheumatology, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles. Dr. Kuhn is a resident in the Department of Radiology, Beth Israel Medical Center, New York, NY. He received his medical degree at the State University of New York Upstate Medical Center, Syracuse, NY.

The Mount Sinai Journal Receives Award

The Mount Sinai Journal of Medicine has won first prize in the 1984 Sandoz Awards for medical journals. The criterion for the award is readability as expressed in overall design, graphics, and editorial qualities. One judge described *The Mount Sinai Journal* as "totally functional . . . designed for reading, with a flawless choice of typeface, length, and leading. Research findings are delivered in large format in two-column book style good enough since Gutenberg . . . graphic interest weighted entirely to content and editorial competence."

The prize was given for all six 1984 issues of the *Journal*. The award, $500 and a certificate, was presented at the Mount Sinai Medical School awards ceremony on the day of commencement, May 31.

Ezra M. Greenspan, M.D., clinical professor of Medicine and associate chief, Division of Medical Oncology, Mount Sinai School of Medicine, and medical director, Chemotherapy Foundation, Inc.

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Combination Cancer Chemotherapy

From a symposium in honor of Ezra M. Greenspan, M.D., on his 65th birthday

Held April 25, 1984 at the Mount Sinai Medical Center, New York

Sponsored by the Department of Neoplastic Diseases, the Division of Medical Oncology of the Department of Medicine, and the Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine (CUNY)

Introduction

Two chairmen of the Department of Medicine at The Mount Sinai Hospital, Drs. George Baehr and Isadore Snapper, were Ezra Greenspan's early mentors and supporters. Snapper, who was the first exponent of chemotherapy for multiple myeloma (stilbamidine), chose Ezra Greenspan as his junior associate. After internship and residency at The Mount Sinai Hospital in 1943–1945, Ezra entered the army. In 1946 he ran the first medical service in a general hospital entirely devoted to tumor patients, at Walter Reed Army Hospital. He developed treatment with combinations of nitrogen mustard and high-voltage radiotherapy for patients with lymphoma. He then joined the National Cancer Institute as chief of the Clinical Research unit and, with Emanuel Schoenbach and Abraham Goldin, conducted laboratory studies that formed the foundation for many of the concepts of chemotherapy and the reversal of chemotherapeutic toxic effects.

What followed was the joy that Ezra felt in translating his own animal studies of folic antagonists to patients with cancer. Indeed, he explored vitamin–antivitamin competition and combination chemotherapy in the clinic along lines derived from his own investigations in mice. He showed an early interest in drug safety and in avoidance of toxicity by using citrovorum factor to reverse the toxicity that could be caused by folic antagonists. Ezra, the first to use stilbamidine for a systemic mycosis (blastomycosis), was also the first to describe fibrosis of the liver from methotrexate.

Ezra returned to Mount Sinai in 1952, where his major contribution was the introduction of clinical combination chemotherapy. He withstood the criticism based on the conservatism that existed at Mount Sinai and elsewhere in the country. He put drugs together, first an alkylating agent and an antimetabolite, and then crossed over to a non-cross-resistant second combination in the treatment of breast cancer.

He submitted his first manuscript on this combination to the *Annals of Internal Medicine* in 1961, but because of skepticism that breast cancer could regress rapidly, the paper was rejected. One reviewer's commentary suggested that the "before" and "after" x-rays were reversed; the second reviewer said that the author of the paper wasn't treating cancer. The third said that combination chemotherapy was too complicated for the average internist to follow. Thus Ezra's initial paper on combination chemotherapy did not appear until 1962, when he reported his results in ovarian cancer in *The Journal of the Mount Sinai Hospital;* in 1963 the *Journal* published his first paper on combination chemotherapy of breast cancer. In all, six of his major papers have been published in what is now *The Mount Sinai Journal of Medicine.* Those observations have been reproduced and verified by many throughout the world. Ezra is well recognized as the pioneer in the combination chemotherapy of breast cancer and ovarian cancer.

Earlier, in 1961, Ezra reported the induction of a second remission in patients with angiosarcoma by the use of cyclophosphamide after refractoriness to thiotepa, thus demonstrating at the clinical level the important principle of non-cross-resistance among diverse anticancer drugs.

His interests are not limited to cancer. He was the first to recognize the value of combining cyclophosphamide and prednisone for the treatment of lethal midline granuloma. This expanded the horizon for the treatment of immunologic disorders; indications for cancer chemotherapeutic compounds in immunologic diseases have been expanding since that time.

Ezra's role as an educator has been apparent through the organization of the Chemotherapy Foundation (in 1968) and its biennial symposia, and through the publication of two editions of his book, *Clinical Interpretation and Practice of Cancer Chemotherapy* (2nd ed., 1982).

Ezra has one characteristic that is unique. Through his ability to impart his own belief and experience in the potential of chemotherapy for the treatment and cure of cancer, he has enlisted the resources of the philanthropic community, and organized the Chemotherapy Foundation. This has been of great importance in Ezra's life. He has devoted much of his time and effort to the foundation. Through the activities of its members, the foundation has been able to exert a major impact on cancer chemotherapy in The Mount Sinai Hospital and in many other institutions in the metropolitan New York area. Indeed, through the foundation's efforts, some three million dollars have been contributed in support of cancer research.

At the Mount Sinai symposium in New York honoring Ezra Greenspan, Dr. Richard Gorlin, chairman of the Department of Medicine at the institution, said of Ezra:

"Another very important emphasis in his study and practice of cancer medicine has been the social and emotional well-being of the patients he cares for. Those who have been under Ezra's care praise him as a physician who really understands the complexities of the problems surrounding cancer as well as the disease itself. He worries endlessly about his patients, not only about giving them the best medical care, but caring about them as human beings as well."

Dr. Howard Bierman, pioneer oncologist, noted: "Ezra has always been a very provocative and productive physician. The name Ezra comes from the ancient Hebrew and means "helper." The ancient Ezra led the Jews to Israel from Babylon. He wrote many of the Hebraic laws. He also created block lettering, which was extremely important because it helped the masses to read and comprehend. That is exactly what Ezra Greenspan has done: he has created an oncologic language which we all understand. Ezra Greenspan has pioneered a field which at the time he began met an unfriendly reception; the field was not acceptable. Knowledge does not mean understanding. To have some kind of understanding often takes a long time. And it took many years for physicians to appreciate the efforts of Ezra Greenspan."

The articles that follow derive from a conference on combination chemotherapy given in honor of Ezra Greenspan on his 65th birthday by a group of experts who have worked closely or in parallel with him in the field he pioneered. The publication of this update and perspective on combination chemotherapy in *The Mount Sinai Journal of Medicine* is appropriate historically, since Dr. Greenspan published the first articles on combination chemotherapy of cancer in this journal.

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Preclinical Chemotherapy: Historical Aspects

ABRAHAM GOLDIN, PH.D., M.DHC.

The history of preclinical chemotherapy reveals an early interest in the triangular interrelationships of host, tumor, and chemotherapeutic agent, agents, or treatment modalities.

Centrality of Host–Tumor Relationship

Clearly, the primary objective has been to increase the selectivity of antitumor action, at the same time minimizing drug toxicity for the host. Attempts to accomplish this have included the search for new antitumor agents with increased antitumor specificity and reduced toxicity for the host; the investigation of drugs and treatment modalities that may avoid the initiation of tumor-cell resistance and will treat more effectively both naturally resistant tumor cells and tumor cells that have become resistant; the unraveling of pharmacokinetic factors in toxicity for the host; and the avoidance of host immunosuppression and the modulation of the host in attempts to exert control over tumor growth and reduce the lethal action of the tumor.

Cognizance of the many factors involved in relationships among host, tumor, and therapeutic agent applies not only to the utilization of individual drugs, but also to the use of combinations of drugs and combined modalities of therapy, including surgical adjuvant chemotherapy, immunotherapy plus chemotherapy, and radiation plus chemotherapy.

Preclinical Systems for Screening New Agents

The discovery in the midforties that nitrogen mustard could exert antitumor chemotherapeutic activity in both the clinic and the preclinical model systems (1–3) stimulated interest in the search for new antitumor agents. Further impetus was provided by the demonstration that the folic-acid antagonist aminopterin was capable of inducing remission in children with acute leukemia (4). Early screening programs included those at the Sloan-Kettering Institute, Southern Research Institute, National Cancer Institute, Chester Beatty Institute, and Army Chemical Center. In the period 1948 through the early 1950s we at the National Cancer Institute, where Ezra Greenspan provided leadership in important chemotherapeutic studies, conducted analyses of different screening procedures as well as structure-activity studies with the nitrogen mustards and colchicine derivatives.

By 1955 the screening systems that had been employed were legion; these were comprehensively reviewed by Gellhorn and Hirschberg (5). The biologic systems included experimental tumors, microbiologic systems, biochemical systems, and systems involving differentiation and development. This myriad of systems was too extensive to adopt in any large-scale screening program, and at the National Cancer Institute, in its primary screening program, leukemia L1210, sarcoma 180, and adenocarcinoma 755 were utilized. Subsequently, varying numbers of experimental tumor models were employed in a spectrum of test systems. Similarly, a spectrum of tumors was utilized in other laboratories, including the Sloan-Kettering Institute, the Chester Beatty Institute, and others (6).

Drugs are capable of retarding and inhibiting tumor growth in experimental tumor systems, and this therapeutic activity can be carried over to the clinic. This clinical potential has been the primary justification for the use of screening systems and attendant drug development programs

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for the discovery and introduction of new antitumor agents into clinical use. As a result of such preclinical programs, new drugs demonstrated to be clinically useful have steadily accrued. So although initially only a handful of drugs—such as the nitrogen mustards, the folic acid antagonists aminopterin and amethopterin (methotrexate), and colchicine derivatives—were available, currently there are many (7).

Dose-Response Relationships

Dose-response relationships are obtained in treatment with respect to both tumor and host, and the choice of proper dosage of drug, among other factors, becomes critical for obtaining maximum therapeutic effect. As the dosage of a therapeutic agent is increased, the antitumor activity is generally also increased. But a dosage is then reached at which the toxicity of the drug for the host becomes dominant, negating the therapeutic effect. This is illustrated for methotrexate, 6-thioguanine, azaserine, and 6-mercaptopurine in the treatment of advanced leukemia L1210 (Table 1) (8). Also, it is possible to compare the relative effectiveness of antitumor agents, and in this study methotrexate was more effective than the other drugs in increasing survival time. In addition, in the comparison of the two analogs 6-mercaptopurine and 6-thioguanine, although the range of drug effectiveness was considerably higher for 6-mercaptopurine, the maximum increases in survival time achieved were similar for the two drugs.

It was on the basis of this type of comparison that methotrexate was determined to be more effective than aminopterin in the treatment of leukemia L1210, which provided a basis for the use of methotrexate in the clinic (9).

TABLE 1
Treatment of Advanced Systemic Leukemia L1210

Drug	Optimal daily dose (mg/kg)	Median survival time (days)	Increase in life-span (%)
Methotrexate	0.9	26.0	116.6
6-Thioguanine	7.0	19.5	62.5
6-Mercaptopurine	180.0	20.0	66.6
Azaserine	53.0	17.0	41.6
Controls	—	12.0	—

Daily treatment initiated 9 days after leukemic inoculation. Leukemic cell inoculation intramuscular in right hind leg. Treatment subcutaneous.

Adapted from Cancer Res 1961; 21:1334–1351.

In another example, both 6-mercaptopurine and cyclophosphamide progressively inhibited growth of subcutaneously inoculated adenocarcinoma 755 with increasing dosage. But the survival time of the animals was increased progressively only to the point where drug toxicity for the host became dominant; with higher dosage, the survival time diminished (8).

Curing Animals with Advanced Metastatic Neoplasia

In the testing of a series of folic-acid antagonists, 3′5′-dichloromethotrexate and 3′-bromo,5′-chloromethotrexate were found to be considerably more effective than methotrexate in increasing the survival time of mice with advanced leukemia L1210, when only a few days of life remained for untreated animals. Both the halogenated derivatives of methotrexate were found to be capable of eliciting extensive increases in survival time of the animals, and a high percentage of the animals were apparently cured of the disease and lived a normal life-span (Table 2) (10). This constituted an initial demonstration that it was possible to cure animals of advanced leukemia L1210, thereby providing encouragement for the clinical investigator in the use of chemotherapeutic approaches for the cancer patient.

The possibility for obtaining cure, even with the use of individual drugs, was fortified further by the demonstration of a linear relationship between tumor-cell kill and the dosage of methotrexate in the treatment of leukemia L1210 (11).

Metabolites and Antimetabolites in Combination Chemotherapy

At an early time, emphasis was placed on studies of metabolite–antimetabolite relationships with respect to both host toxicity and therapeutic effectiveness.

Folic Acid. It was demonstrated in 1949 (12) that folic acid was capable of reversing the therapeutic effectiveness of aminopterin in the treatment of sarcoma 180. However, the relationship of the timing of administration of folic acid to reverse the therapeutic effect of aminopterin was not entirely clarified. In this study, the mice were treated intravenously for a total of 4–6 days. In the groups that received both aminopterin and folic acid, the order of injection was alternated: aminopterin was injected 1 hr prior to folic acid on one day, folic acid was administered 1 hr prior to aminopterin on the second day, and so forth.

TABLE 2
Treatment of Advanced Leukemia L1210 with Halogenated Derivatives of Methotrexate

Methotrexate		3′5′-Dichloromethotrexate		3′-Bromo-5′chloromethotrexate	
Daily dose (mg/kg)	Survivors 100 days	Daily dose (mg/kg)	Survivors 100 days	Daily dose (mg/kg)	Survivors 100 days
2.30	0	200.0	0	200.0	0
1.84	0	160.0	0	160.0	0
1.47	0	128.0	0	128.0	0
1.18	0	102.0	1	102.0	8
0.94	0	81.9	8	81.9	6
0.75	0	65.5	6	65.5	4
0.60	0	52.4	6	52.4	8
0.48	0	41.8	4	41.8	4
		33.5	5	33.5	4
		26.7	4	26.7	4
		21.4	2	21.4	2
		17.1	4	17.1	2
		13.7	1	13.7	0
Total	0/80		41/130		42/130

Treatment daily from day 8 after leukemic inoculation. Ten mice per group. Leukemic inoculation intramuscular in right hind leg. Treatment subcutaneous.
Adapted from JNCI 1959; 22:811–823.

Partial reversal was obtained with this schedule, and in additional studies, more complete reversal of the inhibition of sarcoma 180 was obtained when folic-acid administration was begun 1 day prior to the administration of aminopterin.

Since the timing of folic acid and aminopterin administration appeared to be critical, attention was focused on the timing and dosage required for folic acid to prevent aminopterin toxicity. In a detailed study of the temporal relationships, it was observed that the optimal time for the administration of folic acid in relation to a lethal dose of aminopterin was 1 hr prior to administration of the antagonist (Table 3) (13, 14). Folic acid administered 1 hr early (25 mg/kg) completely protected the mice from a lethal dose of aminopterin (10 mg/kg). The extent of protection diminished as the folic acid was administered at earlier times prior to aminopterin. However, when the folic acid was administered simultaneously with or subsequent to aminopterin, protection by the folic acid was essentially completely lost. No protection against aminopterin toxicity was provided by daily administration of folic acid on repeated injection, even when the folic acid was given 1 hr prior to the aminopterin at each injection interval. However, protection from supralethal doses of aminopterin was obtained with folic acid administered 1 hr prior to aminopterin when the drugs were injected at weekly intervals, suggestive of a repair mechanism operating during the 1-week interval.

Citrovorum Factor. Burchenal et al in 1950 (15) observed that citrovorum factor could prevent the therapeutic effects of methotrexate against mouse leukemia. Schoenbach et al in 1950 (16) reported on the reversal of aminopterin and amethopterin toxicity by citrovorum factor in patients. In 1951 Greenspan et al (17) (Table 3) reported that citrovorum factor was capable of affording complete protection against lethal doses of aminopterin when administered either 1 hr

TABLE 3
Influence of Time of Administration of Folic Acid or Citrovorum Factor on Protection against Lethal Toxicity of Aminopterin

Time of administration before or after aminopterin (hr)	% survival from aminopterin toxicity*		
	Folic acid (25 mg/kg)	CF (mg/kg)	
		75	53.25
−24	50	100	30
−12	60		
−8	70		
−3	70		
−1	100	100	100
0	10	100	
+1	20	100	100
+3	0		
Aminopterin alone (10 mg/kg)	10	10	

* Ten mice per group.
Adapted from Cancer 1950; 3:856–963; Cancer Treat Rep 1978; 62:307–312; and Cancer 1951; 4:619–625.

prior to or concomitantly with the antagonist. A linear relationship was demonstrated between the median lethal dose (LD_{50}) of aminopterin and the dose of folic acid administered, when the folic acid was injected 1 hr prior to aminopterin. Simultaneous administration of the drugs afforded no protection by folic acid, and the LD_{50} for folic acid plus aminopterin was the same as that for aminopterin alone (Table 4) (14, 18). A linear relationship was obtained between the LD_{50} of aminopterin and the dosage of citrovorum factor when the drugs were administered simultaneously (Table 4) (14, 18).

The effect of pretreatment with aminopterin on the subsequent protection afforded by folic acid against aminopterin toxicity 24 hr later was investigated (Table 5) (14, 18). After pretreatment with a relatively low dose of aminopterin (0.1 mg/kg) on the first day, folic acid administered 1 hr prior to aminopterin on the second day did not result in any significant increase in the LD_{50} of aminopterin as compared with corresponding pretreated groups that were subsequently treated with aminopterin alone.

Similarly, after pretreatment with folic acid 1 hr in advance (25 mg/kg) plus aminopterin (0.1 mg/kg) on day 1, no protection was afforded on day 2 by 25 mg/kg folic acid 1 hr early plus aminopterin. Also, after pretreatment with citrovorum factor and aminopterin simultaneously on the first day, no protection was afforded by folic acid 1 hr early plus aminopterin on the next day (18).

In contrast to the results with folic acid, after pretreatment with aminopterin on day 1, treatment with simultaneous citrovorum factor plus aminopterin 1 day later resulted in significant increases in the LD_{50} (Table 5) (14, 18). After pretreatment with folic acid 1 hr early or citrovorum factor simultaneously with aminopterin, protection was also afforded the next day by simultaneous administration of citrovorum factor plus aminopterin. This protection was reduced markedly only when the pretreatment dose approached that of the LD_{50} of aminopterin alone.

There was progressive loss of protection as the citrovorum factor was administered at progressively later intervals subsequent to aminopterin (Table 6) (14, 18). With a fixed dose of citrovorum factor (7.5 mg/kg) the LD_{50} was only moderately higher than that observed with aminopterin alone when the delay was 24 hr. However, even with the 24-hr delay after aminopterin, a tenfold increase in the dose of citrovorum factor (75 mg/kg) resulted in a definitive increase in the LD_{50} of aminopterin (LD_{50} 17 mg/kg) as compared with aminopterin alone (LD_{50} 5 mg/kg). But when the high dose of citrovorum factor (75 mg/kg) was administered 48 hr after aminopterin, there was no significant protection against aminopterin toxicity.

Competitive or Interference Relationships. It could be concluded from these and related in vivo experiments that folic acid acts as a precursor of a citrovorum factor–like substance in the mouse (18). It was suggested that aminopterin acts as an essentially irreversible inhibitor for an enzyme system A involved in the conversion of folic acid

TABLE 4

Relationship between Median Lethal Dose (LD_{50}) of Aminopterin and Dose of Folic Acid or Citrovorum Factor (CF)

Folic acid 1 hr prior to aminopterin (mg/kg)	Aminopterin LD_{50} (mg/kg)	CF simultaneously (mg/kg)	Aminopterin LD_{50} (mg/kg)
0	4.1	0	4.9
2.5	6.8	0.75	8.0
5	11.0	1.88	11.2
15	22.1	3.75	15.8
25	33.1	7.5	24.7

Adapted from Cancer Treat Rep 1978; 62:307–312; and JNCI 1952; 12:987–1002.

TABLE 5

Effect of Pretreatment with Aminopterin on Protection by Folic Acid or Citrovorum Factor against Lethal Toxicity of Aminopterin

Pretreatment, day 0, aminopterin (mg/kg)	Treatment on day 1 with			
	Folic acid* (mg/kg)	Aminopterin LD_{50} (mg/kg)	CF† (mg/kg)	Aminopterin LD_{50} (mg/kg)
0	0	5	0	4
0	25	26	7.5	26
0.01	0	4	—	—
0.01	25	18	—	—
0.1	0	4.3	0	3.5
0.1	25	3.5	7.5	24
1.0	0	1	0	1.0
1.0	25	1	7.5	18
2.0			0	0.5
2.0			7.5	14
4.0			0	0.5
4.0			7.5	3

* Administered 1 hr prior to aminopterin on day 1.

† Administered simultaneously with aminopterin on day 1.

Adapted from Cancer Treat Rep 1978; 62:307–312; and JNCI 1952; 12:987–1002.

TABLE 6
Effect on Lethal Toxicity of Aminopterin of Administration of Citrovorum Factor at Progressively Later Intervals

Timing of CF (hr after aminopterin)	Aminopterin LD_{50} (mg/kg) with CF at 7.5 mg/kg	CF at 75 mg/kg
0	29	
+1	27	
+3	24	
+8	7	
+24	8	17
+48	6	
Aminopterin alone	4.5	

Adapted from Cancer Treat Reports 1978; 62:307–312; and JNCI 1952; 12:987–1002.

to a substance that has citrovorum-factor activity. This inhibitory action appeared to be irreversible and very rapid. The administration of folic acid 1 hr prior to aminopterin appeared to be the period during which the metabolic conversion to a citrovorum-factor–like product occurred. The citrovorum factor in turn demonstrated competitive action for an enzyme system B, as illustrated by the linear relationship of the LD_{50} of aminopterin with dosage of citrovorum factor on simultaneous administration of the drugs. However, it was indicated that the inhibition of enzyme system B by aminopterin was not strictly competitive. It appeared that aminopterin serves as a slowly acting irreversible inhibitor of enzyme system B and that citrovorum factor interferes with the reaction of aminopterin with this enzyme system. This type of competitive relationship has been referred to as "interference" by Ackermann and Potter (19). It should be stressed that this analysis was based entirely on experiments conducted in the whole animal. Thus, the whole animal may provide a quite respectable model for the analysis of quantitative dose-response relationships involving metabolites and antimetabolites.

It appears that the toxicity of any dose of a metabolic inhibitor such as aminopterin should take into account the concentration of substrate (citrovorumlike substance in the case of folic-acid antagonists) and the endogenous protection in the host. Thus, the basis for toxicity would be $I/S + C$, where I is the inhibitor concentration, S the substrate added, and C the endogenous protection in the host (expressed in S equivalence) (18, 20).

These investigations led to an examination of the temporal relationships of administration of folic acid and citrovorum factor with folic-acid antagonists. For equal risk in drug-dose mortality, aminopterin alone was more effective in increasing the survival time of animals that succumbed to leukemia than aminopterin with folic acid administered 1 hr early or aminopterin administered concomitantly with citrovorum factor (21). Even though it was possible to use a higher dosage of aminopterin in these combinations, the protection afforded by folic acid administered 1 hr early or citrovorum factor administered concomitantly was proportionately greater for the leukemic cells than for toxicity to the host, so that there was a resultant loss in therapeutic effectiveness.

On the other hand, in further studies reported in 1954 (22), the observation was made that when the administration of citrovorum factor was delayed for 12–24 hr after aminopterin, at equal risk in toxic mortality for the host, the combination was more effective than aminopterin alone in increasing the survival time of the animals. Evidently, the delayed administration of citrovorum factor reduced aminopterin toxicity more extensively than antileukemic effectiveness. Because of this it was possible to use higher dosages of aminopterin with the delayed citrovorum factor, and this in turn resulted in an improved therapeutic response.

This was an important demonstration that the appropriate utilization of a metabolite with an antimetabolite could increase the specificity of action of an antileukemic agent. Similar results were obtained for methotrexate plus delayed administration of citrovorum factor (23, 24), generally referred to as citrovorum factor "rescue." It was also demonstrated that the specificity of action of an antileukemic agent could be influenced by the dosage schedule. Treatment on an intermittent schedule with aminopterin or methotrexate, for example on days 2 plus 6 after leukemic inoculation, allowed a higher dosage of drug, which in turn increased antileukemic effectiveness (25, 26).

A study was therefore conducted (27) to determine whether the two modalities, namely, an intermittent schedule of treatment plus citrovorum factor "rescue," could supplement each other in therapy. This did indeed occur. Treatment with aminopterin on days 2 and 6 after leukemic inoculation plus delayed administration of citrovorum factor (12-hr delay after each dose of aminopterin) was more effective than the intermittent schedule alone or citrovorum factor "rescue" alone. The further advantage in therapy again resulted from the achievement of a higher dosage of aminopterin.

In 1950 (28) I, with my colleagues Greenspan and Schoenbach, reported studies on the relationship of guanine and guanylic acid to the action of guanazolo (8-azaguanine) on lymphoid tumors in mice and rats. Treatment with guanylic acid and to a lesser extent with guanine at increasing dosage produced progressive reversal of the tumor-inhibitory action of 8-azaguanine. At higher dosages both guanylic acid and guanine appeared to exert moderate antileukemic action by themselves. It would be of interest to examine the importance of the temporal relationships of administration, particularly of guanylic acid and 8-azaguanine, with respect to both toxicity for the host and antileukemic effectiveness.

Active Antitumor Agents in Combination Chemotherapy

My colleagues and I evaluated the possibility of increasing the specificity of action of drugs by combining antitumor agents. In 1952 (29), we reported the antileukemic action of combinations of alpha-peltatin, aminopterin, and 8-azaguanine. Treatment of leukemia L1210 with aminopterin plus alpha-peltatin increased survival time over results with the drugs employed individually (Table 7). Similarly, with 8-azaguanine plus alpha-peltatin, greater increases in survival time were obtained than with either drug along (Table 8). Additional studies were conducted with combinations of triethylene melamine (TEM) plus 8-azaguanine or aminopterin, and of nitrogen mustard (HN2) plus 8-azaguanine or aminopterin. Therapeutic response improved with TEM plus 8-azaguanine and HN2 plus aminopterin. These early studies contributed to a quickly expanding interest in combination chemotherapy, not only for combinations of two drugs, but also in polychemotherapy, and also served as a forerunner of surgical, radiologic, and immunologic modalities in combination with chemotherapy.

TABLE 7

Combination Chemotherapy of Leukemia L1210: Aminopterin plus Alpha-peltatin

Daily dose (mg/kg)		Mean survival time (days ± 1 SE)	Tumor volume day 10 (cm^3)
Aminopterin*	Alpha-peltatin†		
0.075	0	14.6 ± 0.4	2.1
0	5	14.1 ± 0.4	1.5
0.075	5	17.4 ± 0.6	0.6
Control		12.4 ± 0.3	3.6

* Aminopterin days 3–11 after tumor implantation.

† Days 3, 5, 7, and 9 after tumor implantation; treatment subcutaneous.

Adapted from Cancer 1952; 5:153–160.

TABLE 8

Combination Chemotherapy of Leukemia L1210: 8-Azaguanine plus Alpha-peltatin

Daily dose (mg/kg)		Mean survival time (days ± 1 SE)	Tumor volume day 10 (cm^3)
8-Azaguanine*	Alpha-peltatin†		
60	0	16.1 ± 0.5	0.8
0	10	11.5 ± 0.5	0.3
0	5	14.1 ± 0.4	1.5
0	2.5	13.0 ± 0.6	2.2
60	10	11.6 ± 1.1	0.3
60	5	17.4 ± 0.6	0.3
60	2.5	17.0 ± 0.4	0.5
Control		12.4 ± 0.3	3.6

* Days 3–11 after tumor implantation.

† Days 3, 5, 7, and 9 after tumor implantation. Treatment subcutaneous.

Adapted from Cancer 1952; 5:153–160.

Summary

This is a brief review of early preclinical investigations in which Ezra Greenspan played a highly important role, in which we were engaged in the development of principles of chemotherapy pertinent to the clinic. The emphasis, even at this early time, was on means for increasing the selectivity of action of antitumor agents. We were able to demonstrate that by careful manipulation of the host-tumor relationship in therapy, it was possible to alter the specificity of drug action by the use of single agents, metabolites in conjunction with antimetabolites, and combinations of antitumor agents. The importance of the body burden of tumor cells in determining the therapeutic outcome became apparent. Overall, it was demonstrated that careful quantitative investigations could be conducted in the whole animal that could answer questions in a definitive manner and would be of interest to the clinic. These early studies provided an important basis and points of departure for subsequent investigations that quickly fanned out in many directions, both in the laboratory and in the clinic.

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Cancer Chemotherapy: Past Is Prologue

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Conceptual changes in cancer treatment take a relatively long time to reach clinical acceptance. Although the efficacy of combination chemotherapy of cancer was first documented in the 1950s in animal tumor models (1–3), it was not until the 1960s that the initial clinical trials were reported (4–6), and it took still another decade for widespread acceptance. Recognition that new preclinical information is ripe for effective clinical application is made by astute clinicians well informed of the knowledge gained from the study of antitumor agents in animal tumor models. The man this symposium honors, Dr. Ezra Greenspan, was in the forefront of the successful preclinical and clinical efforts at combination chemotherapy.

It is hard to believe in the face of the commonality of combination chemotherapy today that it was once therapeutic anathema. But that was the time of the "wonder drugs," such as penicillin, and every disease was expected to have its single "magic bullet." At that time it took not only knowledge and insight, but courage, to write orders in patients' charts for nurses to administer a combination of two or more "poisons of the week," as the antitumor agents were then termed. It also required clinical acumen to properly design clinical trials. Ezra Greenspan had all these attributes, and his recognition by this symposium is well deserved.

Since those early clinical trials of the 1960s, combination chemotherapy has come a long way in palliating, in improving survival time, and in curing some cancer patients. But if past is prologue to today's recognition of therapeutic accomplishments, we must also recognize that much remains to be done. The more common solid cancers remain refractory to cure.

Biochemical Modulation

Most of the past clinical advances with combination chemotherapy have been made on an empirical basis, and doubtless such progress will continue. However, a more rational chemotherapeutic approach—biochemical modulation to manipulate metabolic pathways to improve the selectivity of anticancer agents—appears likely to expedite progress. The concept of biochemical modulation in preclinical cancer chemotherapy studies is not new. Biochemical knowledge has long been utilized in the laboratory to select agents to enhance the potency of known antitumor agents by proper manipulation of the relevant regulatory pathways. Nevertheless, to date, clinical evidence that the application of laboratory-proven concepts of biochemical modulation can indeed achieve more effective and selective clinical cancer chemotherapy has not been forthcoming.

A review of the attempts at clinical investigation of chemotherapy employing biochemical modulation reveals that the experimental design that worked in the laboratory was not properly incorporated into the clinical trial. In the laboratory, the proper sequence, interval, and dosage ratio between drugs, and the schedule were critical elements in the successful preclinical results. These details were usually ignored in the translation of the laboratory findings into clinical trials, and these clinical trials were unsuccessful in reproducing the laboratory results. Some examples are presented below.

Purine Antagonists. The agent 6-methylmercaptopurine riboside (MMPR) can block de novo

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purine synthesis and, thereby, cause a marked rise in intracellular levels of 5-phosphoribosyl 1-pyrophosphate (PRPP). If 6-mercaptopurine (6-MP) is administered after MMPR has induced increased availability of PRPP, an obligatory substrate for the intracellular anabolism of 6-MP to its nucleotides, more 6-MP is converted to its active anticancer state, and greater anticancer activity ensues. The reported preclinical studies stressed that MMPR did not stimulate 6-MP anabolism when the two drugs were given simultaneously. The two drugs had to be given in appropriate sequence (MMPR prior to 6-MP), and with an interval between the drugs of at least 6 hr (7, 8). Pretreatment with MMPR was necessary for enhancement of 6-MP's anticancer activity.

Despite these preclinical caveats, clinical trial of the combination of 6-MP and MMPR was initiated using concomitant administration of the two drugs; it is not surprising that the clinical results showed the combination not to be better than 6-MP alone (9).

Pyrimidine Antagonists. Another example of successful biochemical modulation in the laboratory followed by failure to reproduce similar results in the clinic is the combination of *N*-phosphonacetyl-L-aspartate (PALA) with the pyrimidine antagonist 5-fluorouracil (FUra). PALA, an inhibitor of de novo pyrimidine synthesis (10, 11), favors the competition of FUra for its metabolic targets by lowering the levels of the normal pyrimidine nucleotides that compete with FUra and, thereby, was shown to enhance the antitumor activity of FUra in preclinical studies (12–15). In contrast, the clinical studies with the PALA–FUra combination (16–19) were reported as showing no improvement over the maximum tolerated dose (MTD) of FUra used as a single agent in historical studies.

However, all these clinical studies employed a high dose of PALA, which necessitated administration of a low dose of FUra to avoid toxicity from the combination; the doses of FUra were approximately 50% of the standard dose of FUra alone for the particular FUra schedule selected. The high-PALA, low-FUra dosage ratios employed in the clinic are not desirable. Use of a dose of the modulating agent (PALA) high enough to require a significant reduction of the doses of the effector agent (FUra) is likely to be self-defeating in comparison with historical studies employing MTD doses of the effector agent. PALA, alone, is essentially devoid of clinical anticancer activity and need be administered with FUra only in a low dose capable of biochemical activity.

Preclinical studies have confirmed that low biochemically active doses of PALA, which do not possess independent antitumor activity, can potentiate the antitumor effects of FUra (14). Also, a recent Phase I and clinical pharmacologic evaluation of PALA with FUra has demonstrated that a low dose of PALA (250 mg/m^2) could effectively inhibit pyrimidine synthesis in humans and could be administered 24 hr before FUra at its MTD of 600 mg/m^2 once weekly without causing undue toxicity (20). This, then, is the low-PALA, high-FUra dosage ratio that should be evaluated in the clinic to assess the antitumor activity of this combination in comparison with historical results with FUra alone at its MTD. This should be the clinical approach to properly test the practical clinical utility of biochemical modulation of an effector agent with a therapeutically inactive modulating agent. Namely, administer a clinically tolerable combination with the effector agent at or close to its MTD as a single agent, and with the therapeutically inactive modulating agent at a low but biochemically active dose. Such a low-PALA, high-FUra dosage ratio in a Phase II clinical study has not been reported.

Folate Antagonists. Biochemical modulation has been shown to be the basis for the enhanced anticancer effects obtained in preclinical studies with sequenced methotrexate (MTX) and FUra combinations (21–27). FUra's therapeutic activity is dependent on activation to a nucleotide, and more PRPP can enhance the extent of this conversion of FUra to its active anticancer state. In preclinical studies, improved therapeutic results with the sequenced MTX–FUra combination were documented to correlate with the intracellular accumulation of PRPP from MTX-blocked de novo purine synthesis.

In contrast to the preclinical studies, the clinical therapeutic results from MTX–FUra sequencing have been largely uncontrolled. Further, although the results of some clinical studies appear promising, others do not. For example, no advantage for 1-hr-sequential MTX–FUra compared with simultaneous treatment could be demonstrated (28), and a large number of the reported studies have only this 1-hr interval (23). An optimal buildup of PRPP after MTX administration takes time. Optimal scheduling of the interval between MTX and FUra is clearly greater than 1 hr and is reported to be many hours, for example 18–24 hr. (26, 27).

Thus, more precisely detailed clinical studies in greater conformity with the design of successful preclinical studies are needed to evaluate applications of biochemical modulation to clinical cancer chemotherapy. Saunders (29) has noted, "a fact of scientific life in the United States [is] that with respect to cancer, fundamental biochemical research and applied clinical research have not generally been carried out in a coordinated way." Experimental design including proper controls, sequence, dosage ratios, and proper interval between drugs, as well as determination of the dose of the modulating agent that yields optimal putative biochemical effect, are among the important details that require attention. Dosages and exposure times may be worked out in the laboratory, but unless the details are properly translated in the clinic, the successful preclinical results may not be achievable in the complex clinical situation.

Inhibition of Cellular Repair. Cellular repair mechanisms appear to be an appropriate new target for biochemical modulation in combination cancer chemotherapy. Poly (ADP-ribose), poly adenosine diphosphoribose, is believed involved in the regulation of DNA replication and repair. Poly (ADP-ribose) polymerase, a chromatin-bound enzyme, responds to DNA damage by synthesizing poly (ADP-ribose) from nicotinamide adenine dinucleotide (NAD). NAD is utilized as an ADP-ribosyl donor with elimination of nicotinamide (30). NAD analogs can inhibit poly (ADP-ribose) polymerase, interfere with the DNA repair process, and enhance the cytotoxicity of DNA-damaging agents, for example irradiation and alkylating agents such as *N*-methyl-*N*-nitrosourea and 1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU) (31–38). Documented inhibitors of poly (ADP-ribose) polymerase include such diverse compounds as pyridine analogues (for example, 6-aminonicotinamide, 6-AN, a good inhibitor), and purine analogues (for example 6-mercaptopurine, 6-MP, a much less effective inhibitor) (39).

The agent 6-MP and its analogs, such as methylmercaptopurine riboside (MMPR), can be hypothesized to interfere with the formation of poly (ADP-ribose). NAD, the substrate for poly (ADP-ribose) polymerase, is synthesized in the cell from nicotinamide mononucleotide (NMN) and ATP by an enzyme (NMN adenyltransferase) that is competitively inhibited by a 6-MP metabolite, thioinosine triphosphate (thio-ITP), the result being inhibition of the biosynthesis of NAD. This 6-MP–induced lowering of intracellular NAD levels by thio-ITP has been previously suggested as an important mechanism for 6-MP toxicity (40).

It is of further interest that thio-ITP is an analog of adenosine triphosphate, that it can be methylated in vivo (41), and that methylthio-IMP is also the active form of the anticancer agent MMPR (42). Both 6-MP and MMPR have activity against experimental solid tumors, but MMPR has been shown to be active in a tumor line resistant to 6-MP, as well as in the sensitive 6-MP line (43). Further, although the thiopurines have been shown to have multiple loci of action (41), and although they are considered to function primarily as inhibitors of purine biosynthesis, certain findings (44) do not support this explanation of its anticancer action.

It appears, therefore, not unreasonable to investigate the hypothesis that MMPR may act on tumors by facilitating the inhibition of a DNA repair mechanism involving poly (ADP-ribose), particularly in combination with a strong poly (ADP-ribose) polymerase inhibitor such as 6-AN.

This agent, 6-AN, is the most potent antagonist of nicotinamide (45). In vivo, it may be incorporated into NAD in place of nicotinamide to give the corresponding NAD analog, via an exchange reaction facilitated by the enzyme NAD glycohydrolase, which can remove nicotinamide from NAD (45, 46). The 6-ANAD analog has been demonstrated to inhibit enzymatic reactions in which pyridine nucleotides play a part as coenzymes (46–50). Of pertinence in regard to intermittent weekly chemotherapy, the inhibitory effects of single and repeated injections differ significantly; for example, a single injection of 6-AN produces no effect on the mitochondrial NAD-dependent dehydrogenases, but daily injections may inhibit them (46).

Whatever the schedule of administration, metabolic antagonists do not antagonize all systems dependent on the metabolite to the same degree (50, 51). Moreover, the concentration of the particular NAD-containing enzyme in tumor and normal tissues relative to that of the appropriate NAD antagonist is relevant to selectivity (50, 51): "it should be possible to inhibit an enzyme present in cancer tissue in small amounts, while producing only partial inactivation of the enzyme in tissues containing larger amounts" (52). The concentration of pyridine dinucleotide in neoplastic tissue has been shown to be low as compared to normal tissue (51, 53, 54). Also, the activity of the nicotinamide mononucleotide (NMN) adenyltransferase enzyme, which catalyzes adenyl transfer to NMN and is inhibited by thio-IPT (55), is considerably less in a number of tumors than in comparable normal tissue (56).

On the basis of these observations, it has been proposed that low levels of pyridine nucleotides in tumors would make their neoplastic cells vulnerable to appropriate antagonists (50, 51, 57). Indeed, 6-AN has been demonstrated to have in vivo anticancer activity against a number of experimental neoplasms, including the Walker carcinoma 256, mammary adenocarcinomas 755 and C3H, and lymphosarcoma $6C_3HED$ (51, 58).

Other findings have potential implications for the proposed mechanism—poly (ADP-ribose) inhibition—of augmenting the anticancer activity of certain DNA-damaging agents by inhibiting DNA repair after injury. A striking augmentation of the radiotherapeutic cure rate of a murine solid tumor in vivo by simultaneous administration of 6-AN and 6-MP has been reported (59, 60). Further, 6-AN, alone, selected for trial on the basis of its potential as a poly (ADP-ribose) inhibitor, was demonstrated to potentiate the effects of radiotherapy on L1210 cells in culture (38).

In addition to inhibiting purine synthesis, MMPR may have additional sites of action concerned with pyrimidine metabolism. In high dosage, MMPR can decrease pyrimidine ribonucleotide concentrations (61, 62). This finding is compatible with demonstrations that purine nucleosides can feedback-inhibit aspartate transcarbamylase, oratate phosphoribosyltransferase, and dihydroorotase (63–67), enzymes involved in de novo pyrimidine synthesis. Since low-dose PALA can selectively inhibit pyrimidine synthesis in certain tumors (14), it seemed reasonable to attempt to reenforce a high-dosage MMPR block on pyrimidine synthesis by adding PALA to MMPR. Another reason for evaluating the combination of low-dose PALA and high-dose MMPR is that the two compounds are useful modulators of FUra (13), an antitumor agent that could be considered for eventual inclusion in the projected combination chemotherapy.

On the basis of this overall rationale, R. L. Stolfi and R. C. Sawyer and I evaluated (unpublished studies, reported below) the triple combination of PALA + MMPR + 6-AN against solid tumors and found striking regression rates of advanced murine mammary carcinomas.

Materials and Methods

Murine Tumor System. For each experiment BALB/c × DBA/8 F_1 (hereafter called $CD8F_1$) mice bearing a first-generation spontaneous syngeneic tumor transplant were distributed among experimental groups so that mice bearing tumors of approximately equal weight were represented in each group. The mice were weighed before each weekly course of treatment and again at 5 days after each course of treatment. Tumor measurements were recorded at 5 days after each weekly course of treatment.

Tumor Measurements. Two axes of the tumor (the longest axis, *L*, and the shortest axis, *W*) were measured with the aid of a vernier caliper. Tumor weight was estimated as follows:

$$\text{Tumor wt (mg)} = L\ (\text{mm}) \times [W\ (\text{mm})^2]/2$$

Chemotherapeutic Agents. PALA and 6-AN were obtained from the Department of Health, Education, and Welfare, USPHS, of the National Cancer Institute, Bethesda, Md. MMPR was obtained from Sigma Chemical Co., St. Louis, Mo. PALA was dissolved in 0.85% NaCl solution, and the pH was adjusted to 7.2–7.5 with 1 N NaOH before adjustment to final volume. MMPR and 6-AN each were dissolved in 0.85% NaCl solution immediately before use. All agents were administered intraperitoneally so that the desired dose was contained in 0.1 ml/10 gm of mouse weight. A 0.85% NaCl solution was administered to controls.

Treatment Groups. There were seven groups of animals. Three groups received single agents—saline (Group 1), MMPR (Group 2), and 6-AN (Group 3)—at each agent's approximate MTD. A group with low-dose PALA as a single agent was not evaluated, since the PALA low dose (100 mg/kg intraperitoneally per week) has been documented to be nontoxic and nontherapeutic (14).

The double-agent combinations included PALA + 6-AN (Group 4), PALA + MMPR (Group 5), and 6-AN + MMPR (Group 6). The dosages of 6-AN and of MMPR in combination with low-dose PALA was lower than the single-agent MTD. Each double combination was administered at its MTD. In the double- and triple-agent combinations, low-dose PALA was administered 18 hr prior to the other agents because its modulating inhibitory effect on pyrimidine pools has been shown to be both ongoing and biochemically effective during this period (14).

One group (Group 7) received the three agents in the same once-a-week dosages as were employed in the double combinations for the 3 weeks of treatment.

Statistical Evaluation. Student's *t* test was used for statistical evaluation of differences in tumor size between groups. Differences in partial tumor regression rate between groups were compared for statistical significance by chi-square analysis. For all statistical evaluations, differences between groups with $p \leq 0.05$ were considered significant.

Determination of Partial Regression. The initial size of each animal's tumor prior to initiation of therapy was recorded. Tumor size was recorded weekly, and final tumor size was determined 5 days after the third weekly course of treatment by the same observer of the initial tumor size. By convention, partial regression (PR) is defined as at least a 50% shrinkage in the volume of the initially measured tumor lesion, as follows:

$$(\text{Final tumor size/Initial tumor size}) \times 100\%$$

The PR rate per treatment group is expressed as a percentage; that is,

$$\frac{\text{No. of PR/group}}{\text{Total no. of animals/group}} \times 100\%$$

The same degree of caliper error is usually made by a single observer in repeated measurements. Hence, the same observer always performs both the initial and the final tumor measurements.

Results

The Figure and Table record the pooled data from three (two male and one female) experiments with $CD8F_1$ mice bearing advanced $CD8F_1$ mammary tumor first-generation transplants. The tumors were very well advanced, averaging 150 mg when therapy was initiated.

The tumor growth curves of the seven treated groups of tumor-bearing animals over the period of therapy (Fig.) show that 6-AN alone (Group 3), and the double combination of PALA + 6-AN (Group 4), are only capable of inhibiting tumor growth; that is, there is no tumor regression. MMPR alone (Group 2), and the double combinations of PALA + MMPR (Group 5) and MMPR + 6-AN (Group 6), can induce tumor regression, but the effect is transient. In contrast, the triple combination of PALA + MMPR + 6-AN (Group 7) effects profound tumor regression throughout the treatment period, with only modest weight loss and with no mortality.

The average final size (100 mg) of the tumors of Group 7 was significantly smaller ($p = 0.01$) than that of tumors in the next most inhibited group, Group 6 (Table). More important evidence of the effectiveness of the triple combination is that very few (essentially no) partial regressions occurred in Groups 1–5 (Table). The next best PR rate was in Group 6, which evidenced, however, a PR rate of only 17%. In striking contrast, the combination of all three agents, in Group 7, yielded a 61% PR rate.

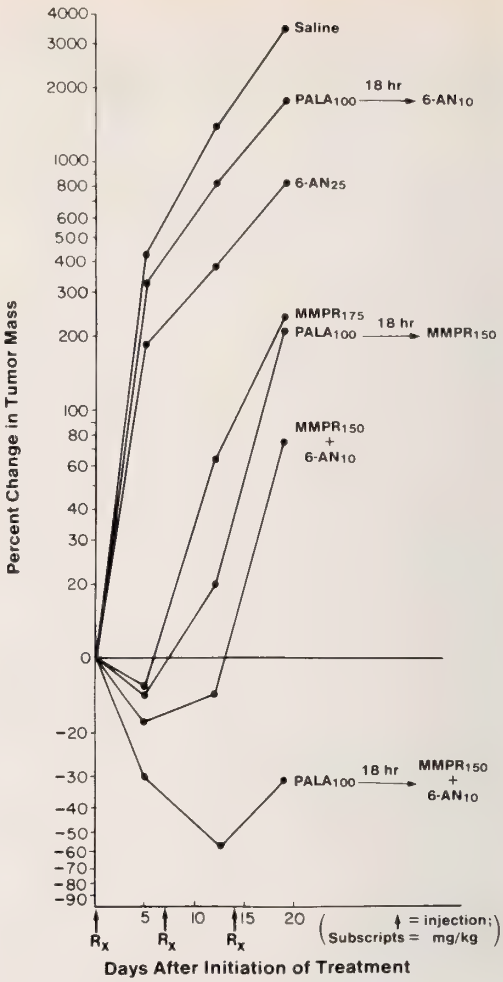

Fig. Combination therapy with *N*-(phosphonacetyl)-L-aspartate (PALA), 6-aminonicotinamide (6-AN), and 6-methyl-mercaptopurine riboside (MMPR) on first generation $CD8F_1$ advanced murine breast tumors averaging 150 mg when therapy was initiated.

Discussion

The high rate of partial tumor-regressions produced by the combination of the three agents PALA + 6-AN + MMPR is impressive, particularly since these striking antitumor effects were induced on very large tumors. Two agents, MMPR and 6-AN, were selected for evaluation on the basis of the rationale that the MMPR + 6-AN combination would damage DNA repair mechanisms by inhibiting poly (ADP-ribose) synthesis. Biochemical evidence for or against this supposition as mechanism needs to be gathered. Clearly, a number of NAD biochemical pathways other than poly (ADP-ribose) could be affected.

TABLE

Combination Therapy with N*-(Phosphonacetyl)-*L*-Aspartate (PALA), 6-Aminonicotinamide (6-AN), and 6-Methyl-Mercaptopurine Riboside (MMPR)*

Treatment*	Tumor wt (mg)		Partial regression		Percent body wt change	Dead/total
1. Saline	5,301	$p = 1.2 \times 10^{-11}$	0/29		+17	4/29
2. MMPR$_{175}$	505		0/30		−3	0/30
3. 6-AN$_{25}$	1,369	$p = 0.03$	0/30		−25	5/30
4. PALA$_{100}$ $\xrightarrow{18\text{ hr}}$ 6-AN$_{10}$	2,765		0/30		−3	10/30
5. PALA$_{100}$ $\xrightarrow{18\text{ hr}}$ MMPR$_{150}$	454		2/28 (7%)		−14	2/28
6. 6-AN$_{10}$ + MMPR$_{150}$	261	$p = 0.01$	5/29 (17%)	$p = <0.01$	−11	0/29
7. PALA$_{100}$ $\xrightarrow{18\text{ hr}}$ 6-AN$_{10}$ + MMPR$_{150}$	100		17/28 (61%)		−22	0/28

Pooled data from three experiments in first-generation CD8F1 advanced breast tumors (Experiments 1164, 1170, 1171) averaging 150 mg when therapy was initiated.

* Three courses of the indicated treatment were administered with a 1-week interval between courses. Subscripts = mg/kg. Observations 5 days after third course of treatment.

However, as discussed above, many NAD-dependent dehydrogenases require daily 6-AN therapy for adverse effects to ensue (46), in contrast to the once-a-week intermittent treatment schedule employed in these studies.

Neither 6-AN nor MMPR produced any partial tumor regressions as single agents. Even in double combination, they produced partial regression rate of only 17%. This relatively minor objective response rate is not surprising, because specifically induced and extensive, potentially lethal DNA damage would be required before inhibition of repair mechanisms surfaced in more evident cytotoxic tumor damage.

However, a degree of DNA damage can and does occur normally without being specifically and extensively induced by such exogenous agents as radiotherapy or alkylating agents. For example, mutations may be created by spontaneous deamination of cytosine residues during the lifetime of a DNA molecule; indeed, direct measurements of the rate of deamination of cytosine to uracil in DNA have indicated that this process occurs at a significant rate under physiologic conditions. Further, misincorporation of the wrong pyrimidine, uracil instead of thymine, into DNA is a common phenomenon, requiring removal and repair of dUMP residues that have been accidentally incorporated instead of dTMP into newly synthesized DNA (68–72).

Incorporation of uracil in DNA and its subsequent removal can cause strand breakage and lead to the production of small DNA fragments (73). Correction requires the availability and utilization of thymine. The pyrimidine-lowering effect of the combination of PALA plus high-dosage MMPR (61, 62) limits thymine availability, and this depletion may augment DNA damage by limiting the repair of DNA-containing accidentally introduced uracil residues. Thus, the damage induced by failure to complete the repair of uracil-containing DNA, due to the combination of PALA and high-dosage MMPR, might further contribute to the damage caused by the inhibition of poly (ADP-ribose) repair mechanisms postulated as the mechanism of the antitumor effects of the MMPR–6-AN combination. Examination of the specific biochemical effects conjectured as the important mechanisms of action for these agents is in progress.

Clinical evaluations of 6-AN as a single agent were undertaken in the early 1960s, then abandoned owing to toxicity (74). However, these studies employed 6-AN on a schedule of daily administration to toxicity. As discussed above, an intermittent schedule is preferable and should be either nontoxic or much less toxic. Moreover, 6-AN toxicity gives warning, in the form of mixed B-complex vitamin "deficiency" signs that are related to the ocular and oral symptoms, before levels dangerous to the central nervous system are reached (74). This warning is advantageous. The early toxic changes may be reversed by stopping the drug and administering nicotinamide. No 6-AN–induced alterations in hematopoietic, hepatic, or renal function were discerned. A new clinical trial of 6-AN, both alone and in combination with other agents, particularly MMPR, on an intermittent schedule seems feasible and indicated.

Summary

Although the utility of biochemical modulation to manipulate metabolic pathways to improve the selectivity of anticancer agents has been well documented in preclinical studies, clinical trial of these concepts has in general been disappointing. These clinical studies employing biochemical modulation are reviewed, and it is concluded that the experimental design that produced successful results in the laboratory was not properly incorporated into the clinical trial. Sometimes, an inappropriate sequence of drugs was employed (for example, MMPR simultaneously with 6-MP, rather than in sequence before 6-MP). Sometimes, an inappropriate dosage ratio between modulating agent and effector agent was employed (for example, high-dose PALA with low-dose FUra, rather than the reverse). And, sometimes, an inappropriate interval was employed between agents (for example, MTX only 1 hr prior to FUra, rather than with an optimal many-hour interval). Therefore, there is reason to believe that biochemical modulation still awaits appropriate clinical trial.

Preclinical studies presented here indicate that the cellular repair mechanisms that involve poly (ADP-ribose) may be an important target for biochemical modulation in cancer chemotherapy. The biochemical rationale for combining MMPR and 6-AN to interfere with poly (ADP-ribose) formation is presented, along with the biochemical reasons for adding PALA to the double combination. Although the biochemical studies to test this hypothesis have not yet been accomplished, the biologic results are impressive. In vivo administration of the triple combination of PALA + MMPR + 6-AN produces striking regression rates of advanced murine mammary carcinomas.

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Multiple Primary Neoplasms and Tumor Diathesis

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The elimination of cancer depends on effective prevention, admittedly a difficult task . . . but cancer is vulnerable to attack! We have learned much about cancer susceptibility from animal studies employing strains which have a high probability of developing specific types of cancer. Certainly, comparable human studies would be even more rewarding if we could identify a population with a high probability of developing cancer.

Multiple Primary Neoplasms

Cancer patients have already proven their susceptibility to malignant disease, and many of them will develop multiple primary neoplasms (MPN). There is an extensive literature on MPN, 482 references in 1983 alone. An intentionally incomplete sample of this literature (1–8) is presented here (Table 1).

The *International Classification of Diseases, Adapted* (ICDA) codes were extensively revised in 1950. Classifications of neoplasms prior to that time have hindered interpretations of the earlier data (9). Nevertheless, the data show remarkable consistency of incidence of MPN. Spratt (3) emphasized that although synchronous MPN constituted 3.1% of all neoplasms studied, nonsynchronous MPN averaged 23.1%. Cook (2) reviewed 46,390 single primary cancers and 4,271 multiple primary cancers. Of 561 possible correlations, only 12 paired sites were confirmed (Table 2). The data at that time were inadequate to support a hypothesis that a single cancer entails a predisposition to develop other cancers. The United States experience on MPN was summarized in 1977 (10) and updated in 1982 (11). The studies of MPN emphasize that the quality of the data required for the documentation of MPN is critically important.

In brief review, the literature on MPN emphasizes that benign and malignant neoplasms may be single, multicentric, or multiple. They may occur in single or in paired organs. Neoplasms may develop in associated organs (for example, ovary, uterine fundus, cervix) or nonassociated organs. By definition, neoplasms occurring within 1 year of each other are known as synchronous (simultaneous) neoplasms. Those occurring more than 1 year after the preceding neoplasm are known as nonsynchronous.

Factors Affecting Estimates. Many neoplasms contain less than 500 million cells, do not produce clinical symptoms, and are too small to be detected by conventional methods. These subclinical neoplasms certainly outnumber those that surface. Furthermore, in "cured" cases of cancer, we generally assume that all neoplastic cells are removed or destroyed (Fig. 1).

However, patients exhibit recurrences with identical histopathologic features decades later (12–14). The explanation is usually that a slow growth rate leads to a long latent period. In addition, neoplastic cells may remain viable, but are controlled by host defense mechanisms and never surface again. Rapid advances in imaging (CT, MRI, tumor-specific monoclonal antibody studies, tissue spectroscopy) are now revealing subclinical neoplasms after therapy, further increasing the documentation of MPN.

During staging of any malignant tumor, pathologists must define the exact nature of the neoplasm, including a definition of its biologic behavior (tissue enzyme, antigen and secretory studies, and so on) (15). Currently, much valuable data on MPN must be discarded because histo-

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TABLE 1
Tumor Diathesis: Literature Review

Ref. no.	Study period	No. of subjects	Years at risk	No. of pt. with MPN	%
1	1904–1968	240,559		7,453	3.1
2	1940–1957	24,000		393	1.6
3	1940–1961	4,320		998	23.1
4,5	1944–1953	37,580		1,909	5.1
6	1948–1970	19,034	79,061	1,113	5.8
7	1949–1962	41,341	123,531	1,643	4.0
8	1966–1975	17,044		597	3.5

logic verification was not sufficiently pursued. For example, at least 25% of cases of adenocarcinoma of the lung believed to be primary turn out to be metastatic, resulting in overestimation of the occurrence of multiple primary neoplasms (N. Friedman, Cedars Sinai Medical Center, Los Angeles, unpublished observations).

On the other hand, new primary neoplasms may be mistaken for metastases, particularly if both neoplasms have similar histopathologic features. Neoplasms in the infirm and aged population may also go unrecognized. Many reports on MPN have excluded either defined types of cancer or the results of specific detection procedures. Unfortunately, the exclusions are not uniform. For example, neoplasms discovered fortuitously at surgery or postmortem are often excluded, as are all nonmelanoma carcinomas of the skin, in situ carcinomas, and carcinomas in contiguous organs. These omissions certainly lead to a significant underestimation of the prevalence of increased predisposition to neoplasia.

Tumor Diathesis

Nature is trying to tell us something about cancer susceptibility, and patients with MPN actually represent samples of a diathesis—a constitutional predisposition toward a particular state or condition, especially one that is abnormal or diseased. Tumor diathesis is a systemic phenomenon not isolated in any organ or system and involves not only the person but also the family. We still do not know how prevalent this condition is, although the documented numbers are rapidly increasing.

TABLE 2
Tumor Diathesis: MPN Relationships—Multiple Endocrine Neoplasia Types I and II, Cancer Family Syndrome

Squamous	Glandular
Oropharynx—oropharynx	Ovary—endometrium
Oropharynx—skin	Endometrium—breast
Oropharynx—lung	Breast—breast
Larynx—lung	Breast—colorectal
Cervix—lung	Colorectal—prostate
Vulva—cervix	Colorectal—ovary

Many patients and families with tumor diathesis often exhibit a constellation of epiphenomena which suggests a generalized growth abnormality preceding or accompanying clinical cancer. Both malignant and benign neoplasms may play an important role as part of the general growth abnormality. The earliest manifestations, which may include immunologic disorders (16), hemihypertrophies (17), and benign skin lesions (18), may be subtle and may not be recognized as an intimate constituent of the diathesis. Well-accepted examples included in the broad category of tumor diatheses are the cancer-family syndrome (19), familial polyposis (20), and multiple endocrine neoplasms (21).

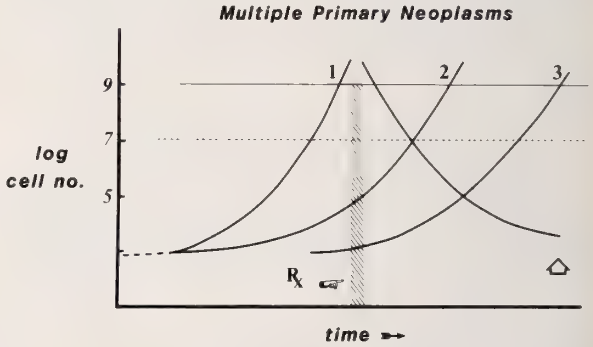

Fig. 1. Sequence of three primary neoplasms. Log cell number of 10^9 is at or below diagnostic level. Stippling represents therapy to subclinical level (arrow). Therapy may influence neoplasm 2 or initiate neoplasm 3.

The common denominator in these disorders is disequilibrium in cell renewal systems. Interference with normal cell growth results in a spectrum of hyper- or hypo-proliferation. The clinical appearance of cancer of the colon, lung, or breast is not an isolated event, but rather the progressive, selective tissue expression of a more generalized systemic process. Tumor-associated diseases, paraneoplastic syndromes, and a vague spectrum of growth disorders (formes frustes) may be part of this generalized neoplastic propensity.

The concept of tumor diathesis should allow physicians to establish predictive profiles (22) so that they may protect the patients and families who share the increased susceptibility. This presents an exceptional opportunity to study the characteristics of predisposition to cancer.

Neoplastic Histories: 25 Patients

Twenty-five patients with tumor diathesis exhibiting 56 malignant neoplasms were selected from my own experience (Table 3). Of 93 benign and malignant neoplasms, 56 were malignant. Benign tumors included angiomas, nevi, polyps, keratoses, papillomas, fibromas, cysts, nodules, myomas, and osteomas. The age of patients ranged from 39 to 85. Person-years of study totaled 292. Twelve patients had a family history of cancer. Ten patients had a history of smoking more than one pack per day. Of the ten smokers, six developed cancer of the lung; one, cervix and ovary cancer; two, urinary bladder cancer, two, cancer of the larynx; two, breast cancer. Three of four patients admitting significant alcohol use had also been smokers.

All 25 patients had nonsynchronous neoplasms within 1 to 21 years (Table 3). Half the total number of second primary neoplasms appeared within 3 to 7 years.

Site-to-Site Association. The initial neoplasm was an adenocarcinoma in 18 patients. The subsequent neoplasms were eight adenocarcinoma and ten epidermoid carcinomas.

Five patients initially had epidermoid carcinomas followed by epidermoid on three occasions, by adenocarcinomas three times, and by non-Hodgkin's lymphoma once. In this small sample, histopathologic features were more determinant than organ-to-organ association.

Synchronicity and Sequence. All the reported data support the observation that nonsynchronous tumors occur many times more frequently than synchronous tumors. In this study there were no synchronous tumors. It is significant that the majority of malignant neoplasms appear more than 1 year apart. Why do patients rarely exhibit more than one malignant neoplasm when different benign tumors in the same host frequently appear in multiples? Is it coincidence? Growth rates? Mortality? Detection? Iatrogenic? Or has the growth of one neoplasm monopolized the capability of other neoplasms to grow?

Certainly, any observation may be the result of coincidence, but in this situation the overwhelming ratio of nonsynchronous to synchronous neoplasia suggests an inviolate series of determinants defining the sequential appearance of tumors.

Tumor Growth Rate. The rate of cell division dictates eventual clinical appearance. Neoplasms have widely differing growth rates which determine their latent periods. Furthermore, current evidence of tumor cell heterogeneity indicates that in a mixed population of cells, only a limited number are actively dividing at any one time (15). The time interval indicates that the second neoplasm is already present when the first neoplasm is detected. The range of 1 to 21 years among the 25 patients mitigates against accepting the growth rate as the only answer (23).

Mortality. Patients who do not survive their first cancer usually do not enter future studies. However, these patients might have second neoplasms determined at postmortem. Such information is not only important for statistical description of tumor diathesis but is also essential in planning a protection program for the surviving family.

Older patients who develop an initial neoplasm may not live long enough for the detection of a subsequent tumor. On the other hand, surviving children and young adults may develop multiple neoplasms because they will live longer.

Age at appearance of the initial neoplasm may influence the sequence of tumors that follow and may be predictive of histopathologic feature. Children surviving leukemias and lymphomas may develop second or third cancers, which are often skin cancers. All patients with cancer, particularly children, must be followed indefinitely.

Detection. We are limited by our vision. The naked eye cannot see a mass that contains less than 500 million cells. A 1-cm neoplasm contains approximately 1 billion cells. If the doubling time of a specific neoplasm is 110 days (colon carcinoma), the neoplasm requires 3,300 days to reach a 1-cm size if all cells survived. A neoplasm is invisible for most of its life.

Preclinical cancer currently is not recognized earlier than the in situ state—an increasingly common event. Many subclinical neoplasms defy detection, may never surface clinically, and are only discovered fortuitously at surgery or at postmortem. Subclinical carcinomas of the prostate (24), thyroid, and kidney (25) are well documented. These multiple neoplasms should be included in reports of tumor diathesis.

Iatrogenic Factors. Most multiple neoplasms will have the same histopathologic features, requiring similar radiation and chemical therapy. That treatment may effectively treat a hidden neoplasm, denying it clinical appearance.

Cancer therapy may directly contribute to an increased risk. Radiation and many antineoplastic agents are immunosuppressive, carcinogenic, and mutagenic (26–28). Recent investigations have documented an increased incidence of

TABLE 3

Neoplastic Histories of 25 Patients

Pt. no.	Patient history						Age (yr)	Ca type	Site	Therapy		
	Sex	Fam	Tob	Alc	Ben	PYO				C	R	S
01	M	−	+	−	+	32	47	Adeno	Lung	−	−	+
							68	N-H lymphoma	—	+	+	−
							72	Epidermoid	Vocal cord	−	+	−
							74	Epidermoid	Skin	+	+	−
02	M	−	+	+	+	9	62	CGL	—	+	−	−
							66	Transitional cell	Bladder	+	−	+
03	M	−	−	−	+	8	78	Epidermoid	Skin	−	+	+
							82	CLL	—	+	−	−
							84	Epidermoid	Skin	−	+	−
							85	Epidermoid	Mastoid area	−	+	−
04	F	−	−	−	−	11	54	Adeno	Mammary	+	+	−
							63	Basal cell	Skin	−	−	+
05	F	+	−	−	+	13	57	Adeno	Mammary	−	+	−
							62	N-H lymphoma	—	+	+	−
06	F	+	+	+	−	9	58	Epidermoid	Mouth floor	−	+	−
							66	Epidermoid	Uvula	−	+	−
							67	Epidermoid	Lung	−	−	−
07	F	+	−	−	+	9	63	Adeno	Colon	−	−	+
							66	N-H lymphoma	—	+	−	−
08	F	−	+	−	−	11	39	Adeno	Lung	+	+	+
							49	Epidermoid	Esophagus	−	−	−
09	F	+	−	−	+	4	46	Adeno	Mammary	+	+	+
							48	Adeno	Pancreas	−	−	−
10	M	+	+	−	−	3	65	Adeno	Prostate	−	+	+
							66	Epidermoid	Lung	+	−	+
11	M	−	−	−	+	15	73	Adeno	Colon	−	−	+
							77	Adeno	Prostate	−	−	+
12	F	+	+	−	−	12	59	Epidermoid	Larynx	−	−	+
							62	Adeno	Mammary	+	−	+
13	F	+	+	−	+	14	61	Adeno	Lung	+	−	+
							71	Adeno	Colon	+	−	+
14	F	−	−	+	−	9	38	N-H lymphoma	—	−	+	−
							43	Adeno	Mammary	+	+	+
15	F	−	−	−	+	6	65	Adeno	Endometrial	−	+	+
							69	Adeno	Mammary	+	−	+
16	F	−	−	−	+	15	48	Adeno	Endometrial	−	+	+
							57	Adeno	Lung	−	−	+
							57	Adeno	Mammary	+	−	+
17	F	+	+	+	+	11	31	Epidermoid	Cervix	−	+	+
							39	Adeno	Ovarian	+	−	+
18	F	−	−	−	+	19	63	Adeno	Endometrial	+	+	+
							78	Adeno	Mammary	+	−	+
19	F	+	−	−	−	10	61	Adeno	Mammary	+	+	+
							70	Epidermoid	Skin	−	+	−
20	F	+	+	−	+	22	46	Transitional cell	Bladder	−	−	+
							50	N-H lymphoma	—	+	−	−
							65	Adeno	Lung	+	−	+
21	F	+	−	−	+	33	38	Adeno	Mammary	−	−	+
							71	Adeno	Colon	+	−	+
22	F	−	+	−	−	3	67	Adeno	Mammary	−	−	+
							68	CLL	—	+	−	−
23	F	−	−	−	+	4	62	Adeno	Mammary	+	−	+
							65	Epidermoid	Lung	+	−	+
24	F	+	−	−	−	5	52	Adeno	Mammary	+	−	+
							54	Epidermoid	Skin	−	−	+
25	F	−	−	−	−	5	47	Adeno	Mammary	+	+	+
							49	Basal cell	Skin	−	−	+

Fam, family history; Tob, history of tobacco use; Alc, history of alcohol use; Ben, benign neoplasms; PYO, person-years observed; Age, age at diagnosis, therapy; C, chemotherapy; R, radiation; S, surgery.

subsequent neoplasms in patients treated with radiation or with chemotherapy, and a higher increased incidence with a combination of both therapies. The subsequent neoplasms are usually lymphomas, leukemias, and nonmelanoma skin cancers, but soft-tissue neoplasms and osteogenic sarcomas often follow radiation (29).

A marked increase in neoplasms often follows immunologic disorders, again, lymphomas, leukemias, Kaposi's sarcoma, and skin neoplasms (16). Moreover, cancer in animals and humans is also immunosuppressive. Surgery, radiation, and chemical therapy further accentuate and prolong that immunosuppression (26, 28). It should be anticipated that for a cancer-susceptible person, therapeutic intervention which increases immunosuppression will enhance the development of subsequent neoplasms. Drugs used in the MOPP program are severely immunosuppressive. Combined with radiotherapy, MOPP results in a 15-fold greater incidence of second malignant neoplasms, largely in myelocytic leukemia. This incidence is estimated to be 5% at 10 years (30).

The annual incidence of second malignant neoplasms 5–15 years after the first neoplasm in nearly 15,000 children seen at ten pediatric oncology centers was 188/100,000, about a ten-fold increase over the age-adjusted expected rate of cancer in the general population. The cumulative probability was estimated to be 3.3% at 20 years (31).

Li reports the frequency of second neoplasms in children to be approximately 20 times higher than the expected rate (32). The cumulative probability was 12%, compared to 0.001% in the general population (11).

On the other hand, some anticancer chemicals may be protective against second neoplasms. Children who have been treated with radiation and chemotherapy for cancer are at increased risk for developing second malignant neoplasms. Unexpectedly, when actinomycin D was included in the chemotherapy, the risk of developing a second neoplasm was decreased by a factor of 7. The risk was reduced still further with repeated courses of actinomycin D. The risk for a second neoplasm was not changed with antifolates, *Vinca* alkaloids, or alkylating agents (33).

Growth Monopoly. Hypotheses concerning the energy requirements of tumor cell growth have waxed and waned. One might consider that the energy to sustain the initial neoplasm might monopolize the growth resources in a patient, denying subclinical neoplasms the ability to enlarge. That restraint would be removed with cure of the initial neoplasm, allowing neoplastic cells of the second neoplasm to divide, leading to its clinical appearance.

Normal growth patterns are highly regulated and interrelated. Paired organs remain similar in size, shape, and function during infancy, childhood, and adolescence. Damaged tissues undergo rapid repair, returning to the original size and shape. Neoplasms are dedicated to a rigid growth pattern unidirected toward an inexorable disaster unless removed or destroyed. These neoplasms dominate the growth potential of many tissues.

Does One Neoplasm Retard Growth of Coexistent or Subsequent Neoplasms?

One may speculate on mechanisms retarding the growth of coexistent neoplasms. Could the mechanism be products generated by the neoplasm or the host? Are immunogenic chemicals or viruses involved? Perhaps transplantation-rejection antigens or growth competition contributes to the final delay.

Products of Tumor or Host. Antineoplastic immunologic components formed against the initial neoplasm may suppress the second neoplasm. The consideration of other nonimmunologic inhibitory factors of unknown description encourages freer thought. These factors may delay the clinical surfacing of the nonsynchronous neoplasm for variable periods. Under appropriate conditions these factors may suppress the original neoplasm, perhaps contributing to spontaneous regression.

Immunogeneration. Impairment of the immune response is associated with increased susceptibility to bacterial, viral, and fungal infections and the development of cancer. Consequently, improved generation and mobilization of the immune processes would reduce that risk. Immunocompetence is dynamic, responding to many antigens if capable. Vaccine immunizations and infections, although selectively specific for each disease entity, also add nonspecific beneficial attributes. Physical fitness adds generally to a prompt and resourceful immune pool. Generalized immune-response stimulants that are reliably antineoplastic are under investigation.

Gene Therapy. Succcessful manipulation and alteration of the gene has transformed speculation into reality (34). It is now possible to remove defective segments of selected genes and to replace them with similar but normal segments using viral vectors. The newly reconstructed normal gene is then cloned for subsequent transplantation into the original host. Although lim-

TABLE 4

Protective and Preventive Agents Proposed for Persons with Tumor Diathesis

Chemical agents	Biologic response modifiers
Nutrients	Blood products
High fiber, low fat	Interferons
Retinoids	Thymosin
Ascorbate	Lymphokines
Tocopherols	Interleukin 2
Trace elements	Transfer factor
Drugs/food additives	Tumor-specific agents
Butylated hydroxyanisol (BHA)	T-cell antigens
Butylated hydroxytoluene (BHT)	Transplantation rejection antigens
Ethoxyquin	Immunotoxins
Diethylthiocarbamates	Monoclonal antibodies
Disulfiram	Immune complexes
Isothiocyanates	Gene alteration
Actinomycin D	Immune stimulants
Hormones and antihormones	Antioncogenes
Anticoagulants	

ited in application now, gene therapy promises to become decisive in all of preventive and protective medicine.

Therapy for Tumor Diathesis Patients

Chemotherapy and Biotherapy. Patients with tumor diathesis should be aware of their risk for developing subsequent neoplasms. They must be informed of programs designed for their protection (Table 4). Of course, they must have the motivation necessary to change life-style and dietary habits and avoid carcinogens and immunosuppressants. This often requires psychological support. Education can encourage realistic awareness and erase hypochondriasis.

Patients are responsible for their own health. This can be emphasized pleasantly by enthusiastic, knowledgeable, and skilled staff who have frequent contact with patients. Detailed records are essential, assisted by self-monitoring via a health diary and regular total-body examinations.

Conclusive statistical data on cancer prevention are highly inferential. For example, 90% of neoplasms of the lung are associated with tobacco smoking. Physicians imply that avoiding tobacco will prevent cancer of the lung. Yet at least 10% of patients with primary pulmonary neoplasms have never used tobacco. Furthermore, most persons who use tobacco do not develop cancer of the lung. One can reason that it is wise to stop smoking because of the increased chances in the patient with a tumor diathesis. Yet we all agree that tobacco is not good for general health.

Diet. In respect to diet as therapy for tumor diathesis, the recommendations are for a prudent food intake to achieve optimal health, but there is no specific anticancer diet (35). Nutrients are chemical therapy. The diet supplies energy for both normal and abnormal cell growth.

Low fat, high fiber, complex carbohydrates, and moderate proteins are advised. Retinoids regulate epithelial growth and thereby have been proposed as a chemopreventive for neoplasms of the lung and skin (36, 37). The antioxidant action of ascorbic acid and tocopherols is believed to be responsible for reduction of selected nitroso compounds preventing formation of potent carcinogens, nitrosamines, and nitrosamides (35, 38). Consequently, ascorbic acid and tocopherol have been proposed as chemopreventives for neoplasms of the gastrointestinal tract.

Of the trace elements, selenium is in the spotlight primarily because an increased cancer incidence was attributed to the low selenium content of the soil (35, 39). Selenium is a cofactor of an enzyme essential for lipid membranes of cells (40). There is no proof that selenium excess is an effective cancer preventive. Selenium intake is largely from dietary cereals, fish, and meat, averaging about 80μg/day (normal, 50–500 μg/day). Selenium toxicity is easily achieved when unnecessary supplements are added to the dietary intake (41).

Food Additives. Numerous additives are consumed daily in processed foods (42). These substances serve as thickeners or stabilizers; flavors and enhancers; emulsifiers; acidulants; chemical leavening agents; colors; humectants; nutritional supplements (vitamins, minerals); preservatives; enzymes, dietary sweeteners (nonnutritive); and sugar. The majority of food additives approved for use have not been tested specifically for carcinogenicity, mutagenicity, or immunosuppressant activity. Many mutagens have not been adequately tested for carcinogenicity. Cooking of meat and fish may produce mutagens, but cooking also destroys pathogens. Many naturally occurring substances in foods are carcinogenic in laboratory animals or mutagenic in bacteria, for example, mycotoxins, plant estrogens, and nitrites. These substances occur in small amounts in the average American diet as it is now constituted.

Biologic Response Modifiers. These investigative agents have shown enough promise in tissue culture and in animals to warrant further study for possible use in humans for prevention. The search for growth-regulatory substances continues. The capability of gene alteration has opened the distinct possibility of corrective gene therapy. Immunologic manipulation has been greatly advanced by cell fusion techniques (43), and monoclonal antibodies and tissue spectroscopy will pinpoint corrective measures to regulate errant enzymes and perhaps regulatory substances.

One of every three of the 234 million people living in the United States—that is, 84 million—will develop cancer in their lifetime. Approximately 2 million people each year will be confronted with malignant disease. This is certainly a significant segment of our population. The goal is to determine which third is at risk. As physicians and patients become better educated, the number of MPN will increase.

Multicentricity of cancer may afford clues to cancer etiology and cancer predisposition or susceptibility. Surgical procedures, for example, contralateral breast biopsies and thorough abdominal explorations, will add a significant number of cases. Approximately 40% of single, detected breast carcinomas have multifocal sites in the single breast. Segmental breast resections produce less data on multicentricity than mastectomies.

Carcinogenesis occurs in multiple stages either in combination or in sequence. When all components are assembled, the result is transformation of the normal cell into a neoplastic cell (44). Tumor diathesis contributes significantly to that transformation. For example, MPN occur frequently in genetically predisposed persons (45, 46). The high-risk patient probably has an ecogenetic (hereditary) sensitivity to environmental and chemical exposure. The earth and its immediate surrounding atmosphere float in the plasma of the universe. The sun is critical to our survival. The high-risk cancer patient may be more susceptible to cosmic radiation or other extraterrestrial events. Solar flares (sunspots) occur about every 11 years and result in increases in cosmic radiation. Two to three years later an increase in melanoma has been observed (47).

We need better comparisons of the frequency and integration of these epiphenomena in the neoplastic and nonneoplastic population. A significant number of patients who have had neoplasms never develop a subsequent neoplasm. Detailed studies of long-term survivors and documentation of the sequence and pathologic features of single and multiple neoplasms in parents, siblings, and progeny would help define patterns of tumor diathesis in families at high and low risk.

The concept of tumor diathesis is a valuable tool which can keep us alert for the earliest detection of cancer and the prevention of its lethal effects.

Summary

Multiple primary neoplasms (MPN) occur frequently and are increasing in number. MPN patients exhibit a tumor diathesis. MPN are significantly underestimated in general practice.

MPN occur synchronously/simultaneously, averaging 3.3%, 1%–5.1%. The remaining patients (95%) either fail to develop another detectable neoplasm or subsequently develop neoplasms nonsynchronously at intervals greater than 1 year. The time intervals ranged from 2 to 21 years between primary neoplasms. Nonsynchronous neoplasms average 23% (15%–35%) depending on type and site of origin. Nonsynchronous MPN occur at least ten times more frequently than synchronous neoplasms.

The nonsynchronous dominance of persons with a tumor diathesis may be due to numerous factors including products of therapy upon the neoplasms and the host. Chemical and biologic agents to be considered for protection and prevention in persons with tumor diathesis are presented. The data to support the effectiveness of some of these agents are not yet conclusive.

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Combination Chemotherapy of Breast Cancer

Richard G. Cooper, M.D.

Breast cancer was first treated with single chemotherapy agents in the early postwar period by Dr. Jeanne Bateman (1), Dr. Jane Wright (2), Dr. Ezra Greenspan, and others (3). In 1963 Dr. Greenspan published his first paper on the use of combination chemotherapy in the treatment of breast cancer (4). This was the first of many reports from Dr. Greenspan on combining drugs that had different mechanisms of action, reports in which he showed a remarkable improved response rate compared to that previously achieved with single agents. Unfortunately, not many people followed his lead. To his credit, Ezra was not discouraged and proceeded with his work in combination chemotherapy; 3 years later he presented a much more elaborate combination of drugs (5) for the treatment of advanced breast cancer: alkylating agents, aminopterin, methotrexate, and Cytoxan combined with hormonal manipulation. Once again he showed an increase not only in number of patients responding to the therapy, but also in length of remission in a variety of patterns of metastatic breast cancer.

Since that time agents tested in the treatment of breast cancer have proliferated. Unfortunately, it was still popular in the 60s and early 70s to use one drug until the patient showed progress and then to use the next agent sequentially. This resulted in a large number of patients succumbing to the original illness because the tumor was resistant to the first agent tried.

We now know that by the time a tumor is large enough to be detected clinically, a significant number of spontaneous mutations can be anticipated. Therefore, it is unlikely that any single agent would be curative in the treatment of breast cancer in its macroscopic state.

In 1969, at the urging of Dr. James Holland and with the support of Dr. Greenspan, I presented data on the combination of Cytoxan, vincristine, prednisone, fluorouracil, and methotrexate (CVPFM) resulting in a high response rate in patients with advanced breast cancer (6). This excellent response rate was in part related to the fact that we were treating patients who had a very high performance status, and that the treatments were given strictly to outpatients under close supervision. We now recognize that this good performance status is indeed the single most accurate predictor of response rates.

After this presentation a multitude of different combinations began to appear in the literature on the treatment of breast cancer; some 67 drugs have now been tested. If these drugs were combinded, we would have at least 48,000 combinations to test—a rather impractical approach. Single agents have produced remissions lasting generally 3–4 months. Combinations of two drugs in patients with advanced disease have produced remissions lasting 7–8 months, and multiple drugs have reportedly induced remissions lasting 12–18 months.

Unfortunately, this gain is not the solution to the problem of breast cancer. There are few long-term survivors among patients who have widespread metastatic cancer, despite the fact that one can induce complete remission in a large majority of them. With the advent of Adriamycin we have the single most active agent in breast cancer. However, in many studies, Adriamycin in combination has shown no significant improvement in number of patients entering remission or length of remission over non-Adriamycin-containing programs, with the exception of the recent reports by the Southeastern Cancer Study Group (7).

Combination chemotherapy regimens will induce good and long remissions in many patients; however, the response rate and the length of re-

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mission are related to several variables, including number and dosage of drugs used, timing of use, sequence of use, and basic status of the patient. Bonadonna's data as well as the data on the use of Adriamycin-containing combinations show a direct correlation (8) not only with number of drugs used, but also with delivery of at least 85% of the anticipated drug dose. One of the advantages of combinations containing prednisone is that this agent raises the blood count so that the chemotherapist can give a larger dose of drug. In addition, we have data that suggest that the crystallographic structure of prednisone is similar to that of methoxyprogesterone and that prednisone, in addition to its effect on blood count, can block progesterone receptors and thus functions as hormonal treatment of certain breast-cancer cells at the same time it is allowing us to give a higher dose of cytotoxic chemotherapy.

Data now show that patients with local chest-wall recurrence treated with successful local treatment do not have a significant increase in life survival (9). Indeed, it is absolutely critical to add systemic therapy to ablative treatment of local lesions. This combination significantly improves both immediate response rate and long-term disease-free survival.

The Management of Primary Breast Cancer

The prognosis for any patient with breast cancer largely depends on the stage of disease at the time of the original diagnosis. A number of variables may predict the outcome for each patient. The most reliable are the number of nodes involved at the time of surgery, the histologic differentiation of the tumor, and the hormone receptors present in the tumor (10).

The first attempt at improving the results of local surgery was the addition of radiation therapy to the axillary and supraclavicular area as well as the internal mammary chain and, in some studies, the chest wall. This additional local treatment did not increase survival, although it did decrease both chest wall and supraclavicular recurrences.

Now patients are again opting to have radiotherapy for treatment of the primary lesion. The critera for this procedure are being refined daily; my own personal criteria are that the tumor should be less than 2.5 cm in size, well-differentiated, and without axillary node involvement. These criteria preselect a good-risk group of patients who will do best by having the breast cancer treated by excisional biopsy and radiation alone. Those patients who have nuclear Grade III lesions with extensive intraductal tumor or independent noninvasive carcinomas near the primary tumor have a high recurrence rate when treated with radiotherapy alone (11).

Adjuvant Chemotherapy

In the past several years (since Ezra Greenspan's pioneering work demonstrating that combination chemotherapy is effective against advanced breast cancer), use of immediate post-operative combination chemotherapy for the patient who has a high risk for recurrence, as suggested by the number of nodal metastases, has become popular. The cyclophosphamide–methotrexate–5-fluorouracil (CMF) program of Bonadonna has significantly improved disease-free survival in patients who have four or less nodes involved and who are premenopausal. Bonadonna has now modified his program and adds both prednisone and Adriamycin–vincristine to treat postmenopausal patients when an adequate dose of CMF is difficult to deliver (12). CMFVP has been effective in uncontrolled and controlled studies in both pre- and post-menopausal women, but tends to lose its effectiveness in patients who have more than ten metastatic nodes, raising the probability of higher tumor burden and more tumor cells that have undergone spontaneous mutation, resulting in resistance to agents that have been used. The combination of fluorouracil, Adriamycin, and cyclophosphamide appears to be effective in patients with ten or more metastatic nodes (13).

Recent data from Bernard Fisher show that in postmenopausal women over the age of 60 who are estrogen receptor positive, the addition of tamoxifen to fluorouracil and L-PAM prolongs disease-free survival (14). Interestingly, L-PAM studies, quoted so frequently in the past, showed that patients who benefited from L-PAM alone were those who had poorly differentiated tumors and would normally have been expected to go downhill rapidly. Patients who had more well-differentiated tumors did not derive any benefit from L-PAM and continued to die at a rate of about 2.5% a year, which is not much different from the control population. Premenopausal women with one to three nodes involved do derive benefit from L-PAM, but only if the tumor is poorly differentiated.

When we look historically at the first studies done, comparing a placebo to thiotepa and to prophylactic oophorectomy, we find two important results: involved axillary lymph nodes are an excellent predictor of recurrence, and patients given thiotepa have a decreased recurrence rate evident at 10 years.

Bonadonna's data on CMF as an adjuvant showed that premenopausal women with four metastatic nodes who received the required amount of chemotherapy (that is, more than 85%) had significantly increased disease-free survival. Unfortunately, the vast majority of postmenopausal women were not able to tolerate the required amounts of chemotherapy. Nissen-Mayer and co-workers reported a 10-year follow-up of a short controlled course of cyclophosphamide given immediately after mastectomy, plus a comparison with radiation therapy followed by cyclophosphamide in a small group of patients (15). These data showed that cyclophosphamide conferred no benefit when it followed radiotherapy. In my report of data on CVFMP with front-end loading of prednisone, I suggested that prednisone destroyed a certain number of hormonally responsive cells, allowing the remaining cells to become kinetically more active and more responsive to cytotoxic chemotherapy. I reported an uncontrolled series compared with mastectomies with or without postoperative radiotherapy in patients with one or more nodes. Disease-free survival of patients with four or more involved nodes increased at least 25%–30%. The drug combination I use is quite similar to that suggested by Ezra Greenspan in the early 60s. In addition, my data showed that the addition of radiation therapy significantly reduced prolonged disease-free periods in patients treated with radiotherapy followed by chemotherapy or treated concomitantly with radiotherapy and a dose of chemotherapy reduced because of hematologic toxicity.

The Southwest Oncology Group has compared L-PAM and CVFMP and has shown a significant benefit to the combination in premenopausal and postmenopausal patients, patients with one to three nodes, and patients with more than four nodes. This was another demonstration that CVFMP is active in the postmenopausal group, confirming my data, and was the first reported controlled series showing effective adjuvant therapy in the postmenopausal group. CALGB studies, comparing yet another modification of this CVFMP protocol in a 2-week on, 2-week off (as opposed to continuous) regimen, against a CMF protocol of Dr. Bonadonna, again showed significant advantage in the five-drug group in pre- and post-menopausal women at all levels of nodal involvement.

My current studies with CVFMP combination chemotherapy suggest that patients with four or more nodes who would normally have an 80%–95% recurrence rate by 10 years will have a recurrence rate of 30%–35% when they are given CVFMP to hematologic toxicity. Indeed, in those patients who receive a full dose of chemotherapy, the recurrence rate is as low as 5%–10%.

We are now faced with patients who do not want to have extensive surgery but still allow us to get all the prognostic information we need, such as in axillary node dissection. Recent data by Edward Fisher suggest that one can correlate histologic findings in the original biopsy with nodal disease. Multiple primary lesions (particularly if one of them is scirrhous) and blood and lymphatic invasion are poor prognostic findings. A positive CEA stain of the primary tumor is often correlated with both poor prognosis (16) and a high chance of nodal involvement, as is the absence of progesterone receptors.

Recent data suggest that when the progesterone receptor is over 100, 5-year disease-free survival approaches 90%, whereas estrogen receptors are prognostically good only for the first 2–3 years and by 5 years have no impact on recurrence rate compared to rates in patients originally estrogen receptor negative (17).

One of the major worries of the surgical community has always been that adjuvant chemotherapy would interfere with wound healing. Animal studies show that the drug dose necessary to impede wound healing is not compatible with survival, and our experience of initiating chemotherapy within 48 hr of mastectomy has never been associated with any problems with wound healing. Thus, I believe we have come full circle now from Dr. Greenspan's original data showing how effective combination therapy can be in advanced disease; combination chemotherapy is now the treatment of choice in the immediate follow-up of patients who have had tumors resected in an effort to induce long-term disease-free survival.

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High-Dose Combination Chemotherapy: Why, How, and When

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Abstract

Some factors that limit the efficacy of chemotherapy, namely, genetic instability, kinetic resistance, and DNA repair in cancer cells, are discussed. Methods of overcoming these limitations are discussed, especially high-dose combination chemotherapy delivered through continuous or prolonged administration. Finally, it is proposed that these aggressive methods of chemotherapy be employed not only for advanced disease but also for occult disease that remains resistant to conventional chemotherapy.

Why High-Dose Combination Chemotherapy?

In order to understand why high-dose combination chemotherapy is mandatory in therapeutic control of cancer, it is appropriate to briefly review the limitations of chemotherapy at the present time and to see how they might be overcome.

Metabolic Resistance. The first limitation, known for years, is metabolic resistance to drugs. This phenomenon has multiple causes, most of them related to genetic mutations which result in new metabolic pathways selected by the treatment administered. Genetic mutations are thought to occur at random, and their number at any point in time is related to tumor size, hence the need for early treatment. But at least three problems, only recently defined, need to be taken into consideration. (a) Some cases of metabolic resistance may be due to gene amplification, such as that induced by methotrexate, which leads to an increase in dihydrofolate reductase, but which may be reversible within a few months, after the methotrexate has been stopped. (b) Apparently, chemotherapeutic reduction of the tumor cell population, which kills the less aggressive clones first, induces an increased phenotypic instability and variability in the surviving clones owing to disappearance of the control exerted by the slow-growing clones, as shown elegantly by Poste and Greig (1). (In addition, chemotherapeutic agents are also potent mutagens.) (c) The chemotherapeutic community has recently learned why patients who fail on treatment A always respond much more poorly to treatment B, to which they have not previously been exposed, in contrast to results when treatment B is given first. Pleiotropic mutants, with multiresistant phenotype, tend to develop in tumors over time, more frequently in metastases. These mutants may be related to the increase in phenotypic instability caused by the imbalance that follows reduction in the cell population.

Metabolic resistance is, at least in part, a quantitative phenomenon. Increasing the intracellular concentration of a drug, or increasing the exposure time of a given concentration, may kill a proportion of cells that, with "conventional" treatment, were not exposed to a sufficient concentration or were exposed to it for too short a time. This should be related to current studies of the membrane permeability of cancer cells manipulated by calmodulin inhibitors and the retention time of drugs in the cells in relation to permeability (2). Whichever of the above mechanisms are at play at any given time in human tumors, the percentage of metabolically resistant cells has been assumed, on the basis of current models (3), to vary with time from 10^{-8} to 10^{-2} against a single agent. These figures are ex-

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tremely high, which would account for most of the chemotherapeutic failures. But in my opinion, these models are still far from the reality. There are several tumors in which combination chemotherapy does not inhibit tumor progression, resulting in a proportion of resistant cells equal to 100%, which seems to be too often the case. However, tumor size is not linearly related to the proportion of resistant cells, as assumed by the models quoted above. The general statement can be made here, for the first time I think, that primary tumors, whatever their size, are more sensitive to chemotherapy than their metastases, as I, along with others, have found when treating lung cancers (4), breast cancers (5), and head and neck cancers (6). These findings are in keeping with the in vitro findings of Poste and Greig (1). Incidentally, they show that chemotherapy may be a very effective locoregional treatment, which lends support to the strategy of preoperative chemotherapy.

Kinetic Resistance. Kinetic resistance is a well-known phenomenon. Phase-sensitive agents, as they are usually prescribed, reach cytotoxic levels in the plasma for only a few hours. Cells that might normally be sensitive to the agent may happen to be in an insensitive phase of the cell cycle during this short period. If the drug employed were effective only against the mitotic phase, the proportion of vulnerable cells at any given time could be as low as 1%.

DNA Repair. Another important limitation of chemotherapy is related to effectiveness of DNA repair after DNA damage caused by intercalating and alkylating agents. Laboratory workers have been aware of this phenomenon for years, but clinicians do not take it fully into account. Our experience in this field was based on various combination schedules with cisplatin as an intercalating agent and bleomycin as an inhibitor of DNA polymerase in patients with various types of cancer, with mainly squamous histology (7). This led us to the indirect conclusion that when a DNA-repair-inhibiting agent is not administered in adequate doses, that is, continuously for 5–7 days after damage, four of five cells may be correctly repaired, which greatly reduces the impact of chemotherapy. This figure is of course only a rough indication of the real situation, but it points to the fact that the chemotherapeutic community at large has, until now, been neglecting an important problem. All the people in our own and related French institutions have been impressed, over the last few years, by the chemotherapeutic power and synergy of the cisplatin-bleomycin combination given continuously for 5 days in a number of tumors (7). However, it should be stressed that this synergism is a two-edged sword. If a myelotoxic agent is used instead of cisplatin, there is an unacceptable level of myelotoxicity.

Toxicity. This leads us to the general problem of toxicity. It has been shown on several occasions that the selectivity of some drugs can be manipulated to the advantage of the host, but in general, toxicity to normal tissue is a major limitation in conventional chemotherapy. It has been the rule for years, under the auspices of the United States National Cancer Institute and the Food and Drug Administration, to reach, in phase I trials, the maximum tolerated dose of a given drug, and then to assess the safe interval between two consecutive courses, in order to define the treatment schedule. I personally tried to break this rule several years ago with CCNU (8), by giving half the maximum tolerated dose twice as often. This trial was successful, but unfortunately we did not draw any general strategic conclusions from it.

With regard to the problem of toxicity and selectivity, it should be stressed again that one of the major differences between normal and tumoral tissue is the fact that, at least in adults, normal tissue proliferates only in order to replace cell losses—physiologic, toxic, or traumatic in origin—whereas tumoral tissue proliferates continuously, probably under the command of growth factors. Under normal conditions the growth fraction in a tumor is usually larger than in normal tissues, and biochemical selectivity, if there is any, must be investigated at this initial stage, prior to the proliferation that occurs in normal tissues as a result of a massive toxic cell loss.

Summary. To summarize the limitations to chemotherapy, it appears that one should be giving several agents without cross-resistance, at their full dose, effective against different phases of the cell cycle, including agents able to inhibit DNA repair, at the same time finding a way to give them without toxicity to the host. This goal has obviously not yet been achieved.

How to Administer

Continuous chemotherapy, made possible by the present generation of portable and implantable pumps, might be a good answer to these problems. Several investigators have already studied the problem of feasibility and pharmacokinetic monitoring of single agents administered for long periods, up to 90 days continuously, but only a few can be quoted here (9–12). In general, it was found that when drugs such as fluorouracil, Adriamycin, *Vinca* alkaloids, bleomycin, cisplatin, and ara-C were used, either the results were superior to intermittent treatment, or the toxicity to normal tissue was much less, or both advantages accrued.

The strategy of prolonged administration appears to overcome some theoretical limitations of chemotherapy.

Metabolic Resistance. Metabolic resistance can be overcome to a certain degree by continuous administration, since the period of exposure is enormously increased. If the plasma level is maintained for several days above the cancer cell tolerance and below the unacceptable level for normal tissues, which of course now has to be worked out for every drug and for every period of administration, it can be assumed that many more cells will be killed than by toxic levels that are maintained for only 6 hr every 3 weeks. In addition, the problem of drug retention related to the multiresistant phenotype would be partially solved, by simply maintaining a prolonged equilibrium between intra- and extracellular compartments. It remains to be determined how several drugs might be combined without cross-resistance over a prolonged period of administration. Our group is working intensively on the technical and scientific problems involved in this situation.

Kinetic Resistance. Kinetic resistance is obviously controlled by prolonged administration insofar as the cells that were previously in an unsensitive phase will be given time to progress to the vulnerable phase and be killed. This is true for a single phase-sensitive agent. Future combinations and/or sequences should be designed in such a way as not to block cells in G1 with drug A that would become sensitive to drug B in S phase. These problems can be solved. The combination of a cell-cycle-active agent for several days and sequences of different phase-active agents each for 2–3 days is a possible solution.

DNA Repair. DNA repair inhibition is achieved only through continuous administration of drugs. In this way the damage-inducing drug prevents repair from occurring. Specific inhibiting agents act in a similar way. They should be given for an even longer time, starting 1 or 2 days after the first drug. It should be remembered that agents such as ara-C, neocarcinostatin, hydroxyurea, isoniazid, and caffeine have been shown to inhibit DNA repair at different levels of the repair system. At the present time, we believe that in some cancers, such as squamous cell cancers, the insensitivity to chemotherapy is much more likely to be due to the effectiveness of the repair system rather than to metabolic resistance.

Toxicity. Finally, toxicity to normal tissues has been shown to be much less, for equal or superior antitumor results, when chemotherapy is administered over a long period. As a matter of fact, larger doses and better results can be obtained without toxicity. At Bobigny, for example, we have been giving cisplatin, 10 mg/m^2/day for 20 days every month, without renal toxicity and with good results. We have also administered bleomycin, 2.5 mg/m^2/day for 20 days, on several occasions with good results. Adriamycin is given at a dose of 6 mg/m^2/day for courses of 15 days without any hematologic problems.

Intermittent Therapy: Obsolete? Here I offer a deliberately controversial statement: intermittent chemotherapy for cancer is obsolete. We are starting to ask our patients to accept permanent treatment, by rotating combinations of nonadditive toxicities. We tend to decrease and suppress rest periods to the limits of host toxicity. There are still some technical problems to be solved and some pharmalogic phenomena to be understood, but more and more patients are accepting these aggressive strategies, which we believe, at the present time, to be a more logical approach.

When to Administer

One of the most important problems faced by the oncologic community at the present time is when to administer high-dose combination chemotherapy.

It has generally been assumed, as shown by our common assumptions if not in writing, that adjuvant chemotherapy should be much less aggressive than chemotherapy for overt metastases. Two different arguments led all of us to this approach: (a) it was assumed, a decade ago, that microscopic occult disease should be easier to eradicate, for kinetic and other reasons, than macroscopic overt disease, thus needing less chemotherapy; (b) it was and still is felt that chemotherapy might be very detrimental to the host and might induce serious damage in patients who would otherwise be cured of their disease by local treatment alone. This had led to several compromises and to the distressing situation that postoperative adjuvant chemotherapy generally has only a modest impact on long-term survival and on the proportion of patients who are really cured of their disease.

There are two answers to the problem of the potential toxicity of adjuvant therapy. First, we personally studied long-term toxicity in 100 patients who had completed 2 years of adjuvant chemotherapy, and found it to be minimal (13). Second, the problem essentially consists of identifying the subsets of patients for whom the potential benefit of a really effective chemotherapy is greater than the advantage of a no-treatment policy that would let the microscopic disease expand and finally kill the host. In this respect, for example, we all have failed, so far, to offer a real treatment to this devastating subset of breast cancer cases with negative nodes and bad prognosis markers such as high nuclear grade or depressed monocyte chemotaxis (14).

As for the doses, and the acceptable level of toxicity, we were all deceived into making the decision, some years ago, that the acceptable toxicity should be less in adjuvant situations than in overt metastatic disease. Patients informed of the natural history of the disease and particularly of their subgroup do accept toxicity and other disadvantages of chemotherapy. As an example, I will take the subset of breast cancer patients who are found to have at least eight involved nodes in the axilla. Presently, at our institution, they are receiving the following rotation therapy: 5 days Cytoxan (CTX), 5-FU, vincristine during week 1; 5 days cisplatin (CIS-DDP), bleomycin (BLM) during week 3; and resuming at the beginning of week 5 for 18 months. This decision was reached on the basis of three different findings: (a) large doses of CTX–5-FU are very effective against metastatic breast carcinoma (15); (b) Cis-DDP–BLM is effective against previously treated breast carcinoma (7); (c) high-dose chemotherapy for inflammatory breast carcinoma is more effective in the long term than conventional doses for adjuvant therapy in positive nodes without inflammatory carcinomas (unpublished data of my own).

It is now well established that metastatic disease results from a highly selective process, and metastatic cells are likely to be more resistant in several ways than primary disease. At the same time, metastatic cells are more actively engaged in proliferation. As I have already pointed out, it may be much easier to obtain complete responses in large primaries than in small metastases.

With respect to the duration of adjuvant treatment, it may very well be that both in oat cell carcinomas with complete response and in resected breast carcinoma, 6 months of therapy has been shown to give results similar to results of 2 years of chemotherapy. All that this means is that when a nonoptimal chemotherapy is employed, there is no advantage to administering it for a long time. A more ambitious attitude would be to direct efforts to finding the optimal treatment, the one for example that will induce complete control or almost complete control, in a given period and then to compare it with treatment of a shorter duration.

Finally, we are left with the problem of when to start chemotherapy in resectable patients. There is no strong evidence on which to base this decision. However, it is known that perioperative chemotherapy can be helpful (16–18). It is also known that resection of the primary tumor is followed by a sharp rise in the labeling index within the metastases. For these reasons I personally think that perioperative chemotherapy should be an arm of various adjuvant trials, followed by postoperative therapy, which should be compared to postoperative therapy alone.

As for neoadjuvant, preoperative therapy, I do not know at the present time whether increasing the control over the primary tumor with powerful chemotherapy, which can easily be done in breast, in head and neck, and even in squamous-cell lung cancer (19), adds anything to the control of occult metastases. At least we know from our experience in lung cancer and from the recent reports by Jacobs et al (20) and Jacquillat et al (21) that unresectable tumors may become resectable, and also that some patients' disease can be controlled with less extensive surgery or no surgery at all, only radiation therapy, which may be of great value for extensive head and neck lesions or breast lesions.

Cancer must be considered a serious disease and should be attacked with more determination with the weapons now available. It seems possible to combine drugs, to increase doses, to improve schedules, to prolong therapy, in ways that should yield better results without more toxicity. It seems advisable to approach so-called early disease with the same determination all of us show for advanced cases.

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Safer Cancer Chemotherapy Using a Kinetically Based Experimental Approach

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Abstract

Improved selectivity of cancer chemotherapy without loss of therapeutic effect can be achieved by direct clinical application of an experimentally based approach giving drugs over 24 hr. The validity of this method has now been established in several tumor types. The advantages of this approach in advanced disease are that full-dose chemotherapy can be given on a regular basis; patients spend much less time on treatment; toxicity to normal tissues, especially bone marrow, is significantly reduced; the need for intensive supportive therapy is drastically reduced; and intensive chemotherapy can be offered without major impairment of the patient's quality of life. For adjuvant treatment, this method permits full-dose intensive chemotherapy to be given early and safely, intervals between the first few courses can be minimal consistent with clinical toxicity, and chemotherapy can be integrated successfully and safely with local therapy. These are the necessary requirements for increased cure rates in certain tumors.

In 1966 W. R. Bruce and his colleagues (1) described a method of administering antitumor drugs in an experimental AKR lymphoma in mice whereby significant selectivity against malignant colony-forming units (stem cells) could be achieved. Two classes of drugs were described. Although selective toxicity against malignant stem cells was noted with drugs from both classes when given over 24 hr, Class II drugs did not increase normal bone marrow stem-cell kill with increasing dose, whereas Class III drugs did increase the kill (Fig. 1).

Clinically Relevant Predictions. These initial studies have been extended to include other drugs and form the basis for a kinetic classification of antitumor drugs. From these original experimental studies various predictions of clinical relevance could be made (2–4). For example:

Optimal tumor cell kill can be achieved without severe bone marrow toxicity.

Marrow toxicity will be less if drugs are given over 24–36 hr in humans.

Marrow toxicity of Class II drugs is related more to duration of exposure than to dose.

Class III drugs in combination will be additively toxic to normal bone marrow stem cells; doses should be reduced proportionately in combinations.

The practice of giving small daily doses of drugs from either class should be avoided.

Extrapolation to Human Tumors. In 1969 we decided to extrapolate this experimental approach directly to the drug treatment of human tumors. Our hypothesis was that if these experimental findings applied to clinical cancer chemotherapy, then a significant reduction in toxicity to normal tissues could be achieved without loss of antitumor therapeutic effect, provided the following medical precautions were always observed:

- Never give another treatment cycle unless the peripheral white-cell and platelet counts have returned to their original levels. If in doubt postpone treatment for 1 week.

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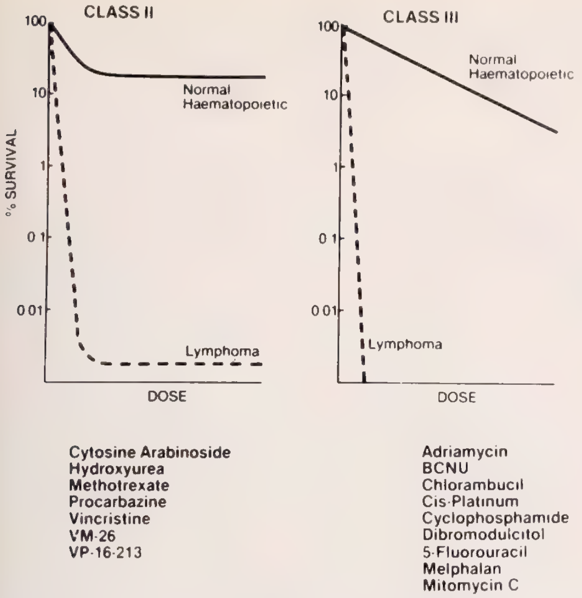


Fig. 1. Kinetic classification of antitumor drugs based on survival of normal hematopoietic and lymphoma colony-forming cells from mice treated with drugs over 24 hr. After Bruce et al (1); reprinted with permission from Price LA, Hill BT, Ghilchick MW, eds. Safer cancer chemotherapy. London: Bailliere Tindall, 1981.

- Patients with impaired renal function receiving methotrexate must have an extended leukovorin rescue (that is, three times longer than normal). Patients with a creatinine clearance of less than 60 ml/min should not be given methotrexate at all.
- Doses of all Class III drugs, for example, cyclophosphamide, Adriamycin, 5-fluorouracil, and cisplatin, should be halved in patients who have received extensive thoracic, pelvic, or abdominal irradiation.
- Adriamycin should not be given to patients with a history of cardiac failure. The total dose of Adriamycin should never exceed 550 mg/m^2. The dose of Adriamycin should be halved in patients who have impaired hepatic function.
- All patients, especially those given drugs that are excreted in the urine, for example, methotrexate, hydroxyurea, and cisplatin, must be adequately hydrated and passing urine, at least 2 L of urine in 24 hr, while they are receiving the drugs.
- Bleomycin should not be given to any patient with impaired respiratory function.
- Combinations containing nitrosoureas, melphalan, or mitomycin C should be given only every 6–8 weeks because these drugs have a delayed effect on bone marrow.

Reduced Toxicity of High Doses over 24 Hours

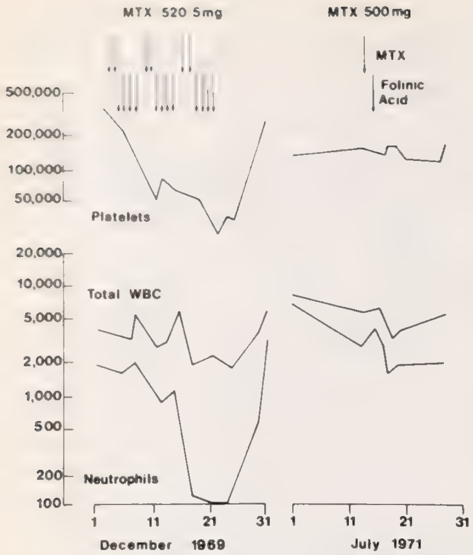
Single Agents. The first prediction from the model was that Class II agents could be given in very high doses over 24 hr with far less toxicity than if they were given in the then conventional fashion over 5 days. We first evaluated the effects of a series of methotrexate infusions in normal saline given in doses varying from 400 mg to 20,000 mg over times varying from 12 hr to 48 hr followed by a folinic acid "rescue." In the eleventh infusion, on August 28, 1969, 20,000 mg was given over 24 hr with no significant reduction in the hemoglobin, total white-cell count, or platelet count and no evidence of mucositis or hepatic damage. This was the first demonstration that such enormous doses of methotrexate could be given safely, and this study has been reported in detail elsewhere (5). However, when the dose was reduced to 7,000 mg but given over 48 hr, definite myelosuppression was observed, coinciding with gastrointestinal tract ulceration as shown by oral mucositis, and liver damage as shown by elevated hepatic enzymes.

The result of giving methotrexate in a thrice-weekly protocol designed by the Medical Research Council to a patient with acute myeloid leukemia (Fig. 2) was life-threatening suppression of the platelet count and absolute neutrophil count, requiring intensive supportive therapy for 1 month. However, when approximately the same dose of methotrexate was given over 24 hr, as described above, no significant myelosuppression occurred and the patient remained in hospital only 2 days.

Combinations. In 1971, we decided to test a second prediction, namely, that combination chemotherapy given over 24 hr would be less toxic than when given according to the then-traditional 5-day protocols. Therefore, we tested a four-drug combination of intravenous cyclophosphamide (500 mg/m^2), 5-fluorouracil (500 mg/m^2), and vincristine (1 mg/m^2), all given at zero time, followed immediately by 200 mg methotrexate infused over 24 hr and a subsequent folinic acid rescue starting at 30 hr consisting of calcium leukovorin, 15 mg orally every 6 hr for four doses.

This pilot study involved 40 patients, 20 of whom had an objective response to chemotherapy (6). However, the most important point is that at no time was there any episode of severe thrombocytopenia or neutropenia, which indicated that intensive chemotherapy could be given safely without loss of therapeutic effect.

This same protocol produced a 67% response



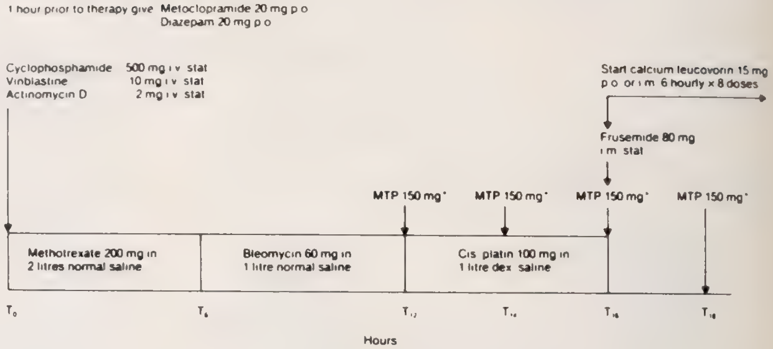

1 hour prior to therapy give Metoclopramide 20 mg p o
Diazepam 20 mg p o
Cyclophosphamide 500 mg i v stat
Vinblastine 10 mg i v stat
Actinomycin D 2 mg i v stat
Start calcium leucovorin 15 mg p o or i m 6 hourly x 8 doses
Frusemide 80 mg i m stat
MTP 150 mg*
MTP 150 mg*
MTP 150 mg*
MTP 150 mg*
Methotrexate 200 mg in 2 litres normal saline
Bleomycin 60 mg in 1 litre normal saline
Cis platin 100 mg in 1 litre dex saline
T_0
T_6
T_{12}
T_{14}
T_{16}
T_{18}
Hours

Fig. 2. **Left** Peripheral blood chart of a patient receiving methotrexate. Note marked toxicity with thrice-weekly regimen and no toxicity with 24-hr regimen. After Price (2), reprinted with permission from Price LA, Hill BT, Ghilchick MW, eds. Safer cancer chemotherapy. London: Bailliere Tindall, 1981.

Fig. 3. **Right** Kinetically based six-drug protocol for treatment of disseminated testicular teratoma.

rate in advanced breast cancer (7), approximately the same as that of the 5-day protocols used at that time, but with significantly less toxicity.

Seven-Drug Study of Squamous Cell Carcinoma. In 1973 we carried out a study of combination chemotherapy in advanced squamous cell carcinomas of the head and neck. The initial pilot seven-drug study program consisted of intravenous Adriamycin 40 mg and vincristine 2 mg at time zero, followed by a bleomycin infusion of 60 mg in normal saline from 6–12 hr. At 6, 9, and 12 hr 100 mg of methotrexate was given as a single intravenous injection (that is, 300 mg in total). At 12 hr 5-fluorouracil was given in a dose of 500 mg. At 18 hr, hydroxyurea, 2 gm, was given orally followed at 24 hr by 6-mercaptopurine, 200 mg orally, and a folinic acid rescue starting at 30 hr consisting of 21 mg of calcium leukovorin orally, given every 6 hr for four doses. Although this protocol produced a 79% response rate in recurrent carcinomas in this region, the number of patients (36) was too small for any statistical conclusions. However, the most important point again was that only one patient had a total white cell count of less than 20,000/mm^2 at any time (8).

Testicular Teratomas. In 1980, we applied the same theoretical principles to the design of a 24-hr protocol for testicular teratomas (Fig. 3). In the first patient, a dramatic response was seen in Stage IV disease with no alteration in the biochemical profile apart from a fall to normal of markedly elevated alpha-fetoprotein and beta-subunit HCG levels. The patient spent only 3 days in hospital for each treatment course, and the maximal fall in the peripheral hemoglobin, white cell, and platelet counts was 12%, 40%, and 50%, respectively, expressed as a percentage of pretreatment baseline levels. This patient was subsequently referred to Dr. L. H. Einhorn at Indiana University for surgical "rescue" and remains alive and well with normal markers at 4 years.

The second patient responded to the same protocol, again with far fewer side effects than customary testicular teratoma programs, but was found on histology reassessment to have a mixed tumor and recurred with increasing tumor markers. He was then treated with VP-16-213 (Vepesid, Etoposide). At that time, the drug was usually given over 3 or 5 days to a total dose of approximately 600 mg. Myelosuppression was said to be a dose-limiting factor. Using the kinetic principles outlined above, this patient was given a 16-hr infusion of 1,200 mg of VP-16-213 in 4 L of normal saline with none of the side effects associated with the 3- or 5-day administration of a smaller dose.

We do not, of course, know whether in the long run these redesigned protocols will produce the same dramatic results as shown by Einhorn and Donohue (9) and others, but this pilot study again validates the predictions made from the experimental model.

Combinations for Lymphomas. Within the last 2 years, we have applied the same theoretical principles to the design of combination chemotherapy for Hodgkin's and non-Hodgkin's lymphomas (Fig. 4). Again, even though the therapy is intensive, in the patients studied myelosuppression is minimal, and although the number of patients is small, there is no apparent reduction of response, compared to other protocols. Seven of nine patients with non-Hodgkin's lymphoma responded, and in a total of 26 treatments the average fall of the platelet count, white cell count, and hemoglobin, expressed as a percentage of pretreatment levels, was 40%, 30%, and 15%, respectively. In two patients with Hodgkin's disease, both of whom responded completely, corresponding figures were 45%, 35%, and 15%. Again, we do not know whether the results of these protocols will in the long term be as effective or durable as the classic DeVita (10) or Bonadonna (11) studies, but they do confirm that the model applies to the treatment of lymphomas.

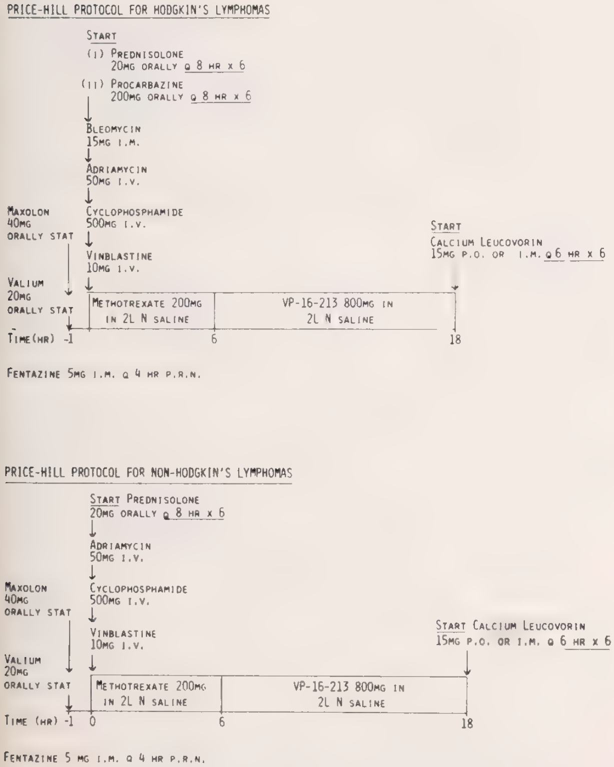

PRICE-HILL PROTOCOL FOR HODGKIN'S LYMPHOMAS
START
(I) PREDNISOLONE
20MG ORALLY Q 8 HR x 6
(II) PROCARBAZINE
200MG ORALLY Q 8 HR x 6
BLEOMYCIN
15MG I.M.
ADRIAMYCIN
50MG I.V.
MAXOLON
40MG
ORALLY STAT
CYCLOPHOSPHAMIDE
500MG I.V.
VINBLASTINE
10MG I.V.
START
CALCIUM LEUCOVORIN
15MG P.O. OR I.M. Q 6 HR x 6
VALIUM
20MG
ORALLY STAT
METHOTREXATE 200MG
IN 2L N SALINE
VP-16-213 800MG IN
2L N SALINE
TIME(HR) -1
6
18
FENTAZINE 5MG I.M. Q 4 HR P.R.N.
PRICE-HILL PROTOCOL FOR NON-HODGKIN'S LYMPHOMAS
START PREDNISOLONE
20MG ORALLY Q 8 HR x 6
ADRIAMYCIN
50MG I.V.
MAXOLON
40MG
ORALLY STAT
CYCLOPHOSPHAMIDE
500MG I.V.
VINBLASTINE
10MG I.V.
START CALCIUM LEUCOVORIN
15MG P.O. OR I.M. Q 6 HR x 6
VALIUM
20MG
ORALLY STAT
METHOTREXATE 200MG
IN 2L N SALINE
VP-16-213 800MG IN
2L N SALINE
TIME (HR) -1
0
6
18
FENTAZINE 5 MG I.M. Q 4 HR P.R.N.

Fig. 4. Twenty-four-hour protocols for Hodgkin's and non-Hodgkin's lymphomas.

Advantages of Kinetic Approach. The advantages of our kinetically based approach for the treatment of advanced disease are these:

Full-dose chemotherapeutic protocols can be administered on a regular basis.

Patients spend much less time in hospital (only one night every 3 or 4 weeks).

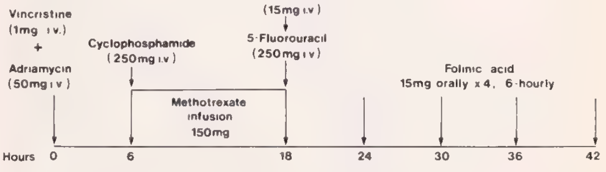
Provided the usual medical precautions are observed, toxicity to normal tissues, especially bone marrow, is markedly reduced.

The need for intensive supportive therapy such as platelet transfusions, isolation techniques, and antisepticemia regimens is drastically lessened. There is no loss of therapeutic effect.

Intensive chemotherapy can now be offered to patients without ruining the quality of their lives. Several other workers have confirmed these advantages in many different "solid" tumors (12–22).

Application to Solid Tumors. Potentially the most exciting use of our experimentally based 24-hr approach whereby intensive chemotherapy can be given with less toxicity than in the past is its application to improving the "cure" barrier for certain "solid" tumors (23). In 1976, an adjuvant chemotherapy study using a five-drug combination for Stage III breast cancer was designed by us for use by the West Midlands Oncology Breast Cancer Group (Fig. 5). The Class III agents were proportionately reduced in dose, but the Class II agents were given in full doses according to the underlying theory.

In retrospect, we feel that the doses of cyclophosphamide and Adriamycin could have been increased safely in this protocol and also that tamoxifen and prednisolone could have been added, although these potential advantages were not known at that time. Even so, compared with other current protocols using one-, two-, or three-agent combinations, our protocol produced far fewer side effects (Table 1). In spite of its greater safety, our five-drug protocol produces comparable re-


Vincristine
(1mg i.v.)
+
Adriamycin
(50mg i.v.)
Cyclophosphamide
(250mg i.v.)
Folinic acid
(15mg i.v.)
5-Fluorouracil
(250mg i.v.)
Methotrexate
infusion
150mg
Folinic acid
15mg orally x 4, 6-hourly
Hours
0
6
18
24
30
36
42

(Price - Hill, 1977)

Fig. 5. Five-drug adjuvant chemotherapy protocol for breast cancer, West Midlands II. Reprinted with permission from Price LA, Hill BT, Ghilchick MW, eds. Safer cancer chemotherapy. London: Bailliere Tindall, 1981.

TABLE 1
Marrow Toxicity of Kinetically Based Chemotherapy Combinations Compared with Other Current Adjuvant Breast Cancer Protocols

Trial	Nausea or vomiting %	Stomatitis %	Cystitis %	Hair loss %	White-cell count/mm^3 2,500–4,000 %	White-cell count/mm^3 <2,500 %	Platelets/mm^3 75,000–100,000 %	Platelets/mm^3 <75,000 %
Bonadonna (24)								
Cyclo + MTX + 5FU	90	25	28	55	67	4	57	14
Fisher (25)								
L-PAM	10	0	0	0	50	12	0	0
Murray (26)								
L-PAM + MTX	43	4	0	3	46	2	6	2
Edelstyn (27)								
Cyclo + MTX + VCR + 5FU	33	2	0	10	22	1	1	0
West Midlands I (19, 28)								
CHL + MTX + 5FU	48	1	0	3	0	0	0	0
West Midlands II (19, 28)								
Cyclo + VCR + ADR + MTX + 5FU	67	3	0	100	0	1	0	0

Cyclo, cyclophosphamide; MTX, methotrexate; 5FU, 5-fluorouracil; L-PAM, melphalan; VCR, vincristine; CHL, chlorambucil; ADR, Adriamycin.

sults in disease-free survival compared with other protocols (24–28), and in advanced disease has a response rate of 70% (29).

Five-Drug Study of Squamous-Cell Carcinoma. In 1975, we modified our original seven-drug protocol for squamous-cell carcinomas of the head and neck to a simpler five-drug protocol (Fig. 6). Two courses of this new protocol given to a series of 200 patients with advanced epidermoid carcinomas of the head and neck *before* "curative" local therapy showed that responders to initial chemotherapy have significantly improved survival compared with nonresponders ($p < 0.006$). Significantly more chemotherapy responders achieved a complete remission after local therapy compared with nonresponders ($p < 0.006$). Complete responders have dramatically improved survival compared with those with residual disease after local treatment. In Stage IV patients who respond to initial chemotherapy and subsequently achieve complete remission after local treatment, there was a significant increase in survival compared with nonresponders at 5 years ($p < 0.001$) (30). Toxicities of our Schedule A protocol compared with some of the more commonly used cisplatin-containing programs are shown in Table 2 (31–36).

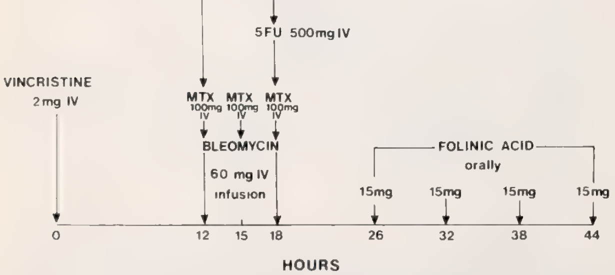


Fig. 6. Initial primary chemotherapy protocol for advanced squamous-cell carcinomas of the head and neck.

Non-Cross-Resistant Combinations. Recently Goldie and Coldman (37) have produced a mathematical model that relates the probability of spontaneously occurring mutations to drug-resistant phenotypes to the size and age of the tumor. This can be related to the probability of curing tumors with chemotherapy. Basically, the probability of drug-resistant mutants is low early in the life of the tumor, but increases progressively with tumor size. Chemotherapy therefore should be given as early as possible in the treatment of the disease, and this theory is in accordance with the pioneering work of animal experimentalists such as Skipper, Schabel, and co-workers (38).

The Goldie-Coldman model suggests that the development of drug-resistant mutants might be delayed by the administration of alternating non-cross-resistant chemotherapy protocols. We are now attempting to design an alternating non-cross-resistant combination chemotherapy program for "upfront" use in adjuvant breast cancer

TABLE 2

Toxicities of Schedule A Compared with Recent Cisplatin-Containing Head and Neck Cancer Protocols

Drug combination	Days on Rx per course	Nausea and vomiting (%)	Significant myelotoxicity (%)	Renal toxicity (%)	Ref
CIS + BLM	9	Moderate	2	9	31
CIS + VCR + BLM	5	71	27	10	32
CIS + BLM	9	100	5	20	33
CIS + VCR + BLM	7	100	2	19	34
CIS + BLM + MitC	5	100	2	0	35
CIS + 5FU	4	66	37	22	36
VCR + BLM + MTX + 5FU	2	10	2	0	30

* CIS, cisplatin; BLM, bleomycin; VCR, vincristine; MitC, mitomycin C; 5FU, 5-fluorouracil; MTX, methotrexate.

studies using the highest doses with the shortest possible duration betweeen treatments compatible with safety. An initial pilot study is shown in Fig. 7. Seventy alternating courses of these protocols have been given to patients with advanced breast disease, and all patients were given tamoxifen, 20 mg twice daily, and prednisolone, 5 mg twice daily, in addition. Protocol 1 was given on day 1, protocol 2 on day 14, and thereafter the protocols were alternated every 21 days. Side effects, as expected, were minimal, and patient compliance was 100%. The major toxicity was to the platelet count with a maximum fall of 55% compared with pretreatment levels. On no occasion was it necessary to delay chemotherapy because of myelosuppression, and no patient required supportive measures at any time. Of the nine patients with measurable disease, five achieved complete remission and four partial remission (39).

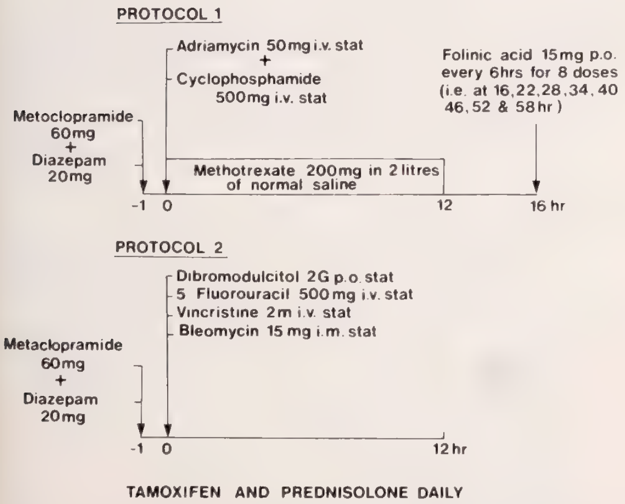

PROTOCOL 1
Adriamycin 50mg i.v. stat
+
Cyclophosphamide 500mg i.v. stat
Folinic acid 15mg p.o. every 6hrs for 8 doses (i.e. at 16,22,28,34,40 46,52 & 58hr)
Metoclopramide 60mg
+
Diazepam 20mg
Methotrexate 200mg in 2 litres of normal saline
-1
0
12
16 hr
PROTOCOL 2
Dibromodulcitol 2G p.o. stat
5 Fluorouracil 500mg i.v. stat
Vincristine 2m i.v. stat
Bleomycin 15 mg i.m. stat
Metaclopramide 60mg
+
Diazepam 20mg
-1
0
12hr
TAMOXIFEN AND PREDNISOLONE DAILY

Fig. 7. Pilot study of alternating non-cross-resistant drug protocols for adjuvant chemotherapy of breast cancer (39).

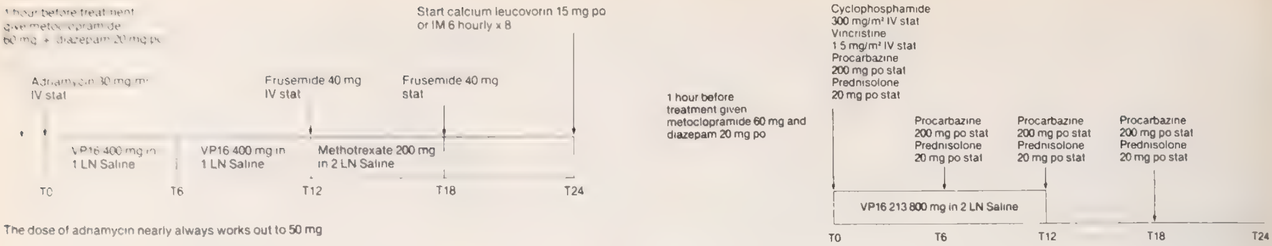
Preradiation Combinations. Recently multiple-combination-chemotherapy regimens alone or combined with chest radiation have produced a significant improvement in median survival and a few long-term survivors in patients with small-cell lung cancer (40). However, some concern has been expressed at the occasionally severe toxicity that occurs when these two modalities are combined in the treatment of this disease (41).

Accordingly, we used our 24-hr approach to design a partially non-cross-resistant alternating program for use before radiation in this disease to see if full-dose chemotherapy could be given with significantly less toxicity and without compromising subsequent radiation. The protocols used are shown in Fig. 8.

Seven courses have been given so far to three patients, all of whom responded, two with complete remissions. The maximum fall of the peripheral white cell count was 50%, the maximum reduction in platelet count 30%, and the maximum fall of hemoglobin 12%, all expressed as a percentage of the patient's own pretreatment baseline levels.

This program is currently undergoing further investigations in a larger number of patients, but it is already clear that our experimentally based approach allows a much higher total dose of drugs within a much shorter time before radiation therapy in small-cell lung cancer.

Although the optimal adjuvant chemotherapy protocols for most tumors are not known, our method makes it possible to integrate intensive chemotherapy safely with radiation or surgery


1 hour before treatment
give metoclopramide
60 mg + diazepam 20 mg po
Adriamycin 30 mg/m²
IV stat
VP16 400 mg in
1 LN Saline
VP16 400 mg in
1 LN Saline
Frusemide 40 mg
IV stat
Methotrexate 200 mg
in 2 LN Saline
Frusemide 40 mg
stat
Start calcium leucovorin 15 mg po
or IM 6 hourly x 8
T0
T6
T12
T18
T24
1 hour before
treatment given
metoclopramide 60 mg and
diazepam 20 mg po
Cyclophosphamide
300 mg/m² IV stat
Vincristine
1.5 mg/m² IV stat
Procarbazine
200 mg po stat
Prednisolone
20 mg po stat
Procarbazine
200 mg po stat
Prednisolone
20 mg po stat
Procarbazine
200 mg po stat
Prednisolone
20 mg po stat
Procarbazine
200 mg po stat
Prednisolone
20 mg po stat
VP16 213 800 mg in 2 LN Saline
T0
T6
T12
T18
T24

The dose of adriamycin nearly always works out to 50 mg

The dose of cyclophosphamide nearly always works out to 500 mg
The dose of vincristine nearly always works out to 2 mg
After day 14, schedules I and II are alternated every 21 days in responding patients

Fig. 8. Left Schedule I (first given on day 1) of a partially non-cross-resistant, 24-hr alternating protocol for initial therapy in small-cell lung cancer. **Right Schedule II** (first given on day 14) of the alternating protocol.

and makes increased cure rates at least possible in carcinomas of the breast, ovary, bladder, small-cell lung cancer, and perhaps prostatic tumors. The advantages of our kinetically based approach for adjuvant chemotherapy are that

- Full-dose intensive combination chemotherapy can be given safely and early.
- Intervals between courses of chemotherapy can be the minimum consistent with clinical tolerance for the first four or five cycles, since there is no severe myelosuppression.
- These chemotherapy protocols can be integrated successfully and safely with surgery and radiation therapy.
- The 24-hr approach can be used in the design of alternating non-cross-resistant treatments.

These are the necessary requirements for increasing cure rates for certain tumors.

It appears from our studies that with concepts and treatment strategies available now, the necessary conditions exist to increase the cure rate in certain solid tumors within the next decade. However, only properly conducted, randomized, prospective clinical trials will determine whether these necessary conditions are sufficient to prolong survival significantly in these diseases.

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Current Status and New Vistas in Combination Chemotherapy

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Abstract

Much of the progress achieved in clinical cancer chemotherapy has derived from the use of agents in combination. The scientific and clinical investigative basis for dose schedule and combination chemotherapy has advanced rapidly. Pari passu with these advances has occurred major progress in treatment. Strategies of combination chemotherapy initially applied to the acute leukemias and lymphomas indicated the importance of remission induction, sanctuary treatment, and treatment of minimal residual disease. More recent strategies have included the cycling of combinations of agents, presuming that cycling decreases the risk of drug resistance; the use of chemotherapeutic agents after control of the primary tumor in patients with high risk of micrometastatic disease; and finally, more recently, the use of chemotherapy as initial treatment (induction chemotherapy) for patients with advanced local disease, with the intent of stage reduction, thus increasing the opportunity of controlling local disease with surgery, with radiotherapy, or with both.

It is an honor to participate in this conference and to recognize the major and seminal contributions that Ezra Greenspan has made to cancer chemotherapy generally and to combination chemotherapy specifically (1, 2). James Holland has made outstanding contributions to clinical cancer therapeutics, particularly in relationship to the curative treatment of acute leukemia. The highly distinguished contributions to clinical cancer research made by my fellow authors in this issue are noted below.

In 1955, Jim Holland, Gordon Zubrod, and I initiated a program designed to identify problems and to construct studies relevant to treatment of acute lymphocytic leukemia in children. At that time, there were several agents capable of producing remission, and there were excellent experimental models of acute lymphocytic leukemia, including those developed and studied by Drs. Goldin and Law. Our first efforts were to construct prospective experimental designs, including quantitative studies involving randomization, specific criteria for selection of patients, and, particularly, objective and quantifiable criteria for measuring response (3). Shortly thereafter, the major difference between the biology and therapeutic strategies for remission induction, treatment during remission, and the problem of central nervous system leukemia were recognized and approached separately. Our first study, among other things, recognized that the most powerful discriminant for improved survival was the attainment of complete remission (3). Unfortunately, complete remissions occurred in a minority of patients.

Increasing the Complete Remission Rate. Since survival is the final arbiter of the effectiveness of treatment, our first goal was to increase the complete remission rate. For this, we turned to the dose effect and, particularly, to combination chemotherapy. In a quantitative study, we found that the combination of methotrexate and 6-mercaptopurine was superior for remission induction to either agent alone, but the advantage was relatively slight (4). Since dose-limiting toxicity for both agents was myelosuppression, the

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TABLE 1
Combination Chemotherapy in Acute Lymphatic Leukemia of Childhood

Agent(s)*	No. of pts	Complete remission		Year started
		No.	% (CRR†)	
MTX	48	10	21%	1958
6-MP	43	12	27%	1958
VCR	81	38	47%	1961
Pred	72	41	57%	1960
MTX + 6-MP	39	17	45% (42%)	1958
Pred + 6-MP	154	127	82% (69%)	1961
Pred + VCR	63	53	84% (77%)	1963

Data from Leukemia Chemotherapy Group B.

* MTX, methotrexate; 6-MP, 6-mercaptopurine; VCR, vincristine; Pred, prednisone.

† CRR, complete remission rate, calculated assuming independent drug action: $CRR_{A+B} = CRR_A + CRR_B\ [(100 - CRR_A)/100]$.

doses had to be substantially reduced when employed in combination. In both experimental and clinical studies, the dose-response curve for most antitumor agents was found to be steep. Accordingly, major emphasis was given to combinations of agents with qualitatively different mechanisms of action, particularly agents with qualitatively different dose-limiting toxicity, so that full doses could be maintained in combination. A sequence of quantitative studies conducted by the Acute Leukemia Group B indicate that combination chemotherapy is highly effective and synergistic, particularly for combinations in which full doses of active agents can be employed (Table 1). Vincristine and prednisone alone, and particularly with the addition of a third agent, now produce complete remissions regularly in more than 90% of patients. Since neither is myelosuppressive, such remissions are rapid and usually unaccompanied by major problems with bleeding and infection (5).

Treatment during Remissions. After the attainment of a high complete remission rate and with the recognition that, even under these circumstances, all patients relapsed within a median time of 7–9 months, the issue of treatment during remission was addressed. It was quickly recognized that prednisone and vincristine alone or in combination, although highly effective in inducing remission, were not particularly effective in maintaining remissions. In contrast, the antimetabolites 6-mercaptopurine and methotrexate, although relatively less effective for inducing remission, prove substantially more effective for treatment during remission. This recognition and the use of a crossover design had major long-range implications for strategies of chemotherapy generally. A sequence of quantitative studies addressed the issue of treatment during remission (Table 2). The first question was whether an agent active in inducing remission would, in fact, be effective in the treatment of microscopic disease, that is, treatment during remission (6). Thus, after complete remission induction, patients were randomly allocated to 6-mercaptopurine maintenance or to no maintenance. A highly significant advantage for 6-mercaptopurine was obtained with respect to duration of remission, indicating the importance of treatment during remission.

The second study addressed the issue of dose; a twofold difference in dose of drugs delivered during remission made a significant difference in duration (7).

The third question had to do with schedule. Experimental studies, particularly by Goldin and associates, demonstrated that intermittent treatment, particularly with methotrexate, was superior to daily treatment in a randomized, comparative study (Table 2) (8). A highly significant advantage for intermittent methotrexate was demonstrated, and to this day, methotrexate continues to be used intermittently in essentially all clinical settings.

The fourth question was the effectiveness of combination therapy. As with remission induction, combinations, particularly involving daily 6-MP with intermittent methotrexate, were superior to single agents. This represents standard remission maintenance, and there is evidence, albeit not conclusive, that other approaches (until relatively recently) may add to effectiveness, such as the addition of cyclophosphamide or intermittent VP.

Further Progress. With these improvements in complete remission induction and maintenance, the duration of survival was substantially improved, but relapses continued to occur in essen-

TABLE 2

Acute Lymphocytic Leukemia—Treatment during Clinical Remission (CR): Key Clinical Trials

Variable	Regimen	Duration CR, median (mo.)	
Active agent (MP)	VP to CR R, then		
	MP	7	$p = 0.01$
	Placebo	1.5	
Schedule	VP to CR R, then		
	MTX daily	4	$p = 0.01$
	MTX 2× wk	9	
Dose	CR induction, then		
	Full*	15	$p = 0.01$
	Half	6	
Combinations, best as of 1970	MTX 1× wk + MP 1× day		
	MTX 1× wk + MP 1× day + CPA		
	Either of these + intermittent VP		

VP, vincristine plus prednisone; MTX, methotrexate; MP, 6-mercaptopurine; CPA, cyclophosphamide.

* Combined MTX, MP, CPA.

tially all patients. However, a progressively increasing number of patients, in some series exceeding 50%, were relapsing initially in the central nervous system. Based on experimental studies of L1210 leukemia, as well as studies of the clinical picture and the pharmacology, the interpretation of the pathobiology of meningeal leukemia is that the central nervous system is probably microscopically involved at the time of diagnosis. Systemic treatment, although producing and maintaining complete remission in the extracranial sites, does not adequately control intracranial disease because the intracranial site is a pharmacologic sanctuary. Therefore, such cells progressively proliferate, usually in the form of sheets along the meninges, and eventually the clinical and laboratory syndrome of increased intercranial pressure and pleiocytosis occurs.

In elegant studies performed primarily at St. Jude's Hospital under Drs. Pinkel and Simone, the use of radiotherapy and intrathecal methotrexate to treat mimimal central nervous system disease markedly decreased the occurrence of clinical meningeal leukemia and produced a cure rate (flat disease-free survival curves) of approximately 40% (9).

During the past decade, further progress in the treatment of acute lymphocytic leukemia has involved intensification of initial treatment, especially combination chemotherapy and the use of asparaginase and Adriamycin; in particular, asparaginase, given intravenously weekly for some 6 months early in remission, has further increased the disease-free survival curve to 80% or 90%.

Related Hematologic Diseases. The importance of combination chemotherapy, dose, and schedule in acute lymphocytic leukemia encouraged extrapolation to related hemotologic diseases, such as the lymphomas. Indeed, the seminal, four-drug study involving vincristine, amethopterin, mercaptopurine, and prednisone (VAMP) for acute lymphocytic leukemia in 1962 was one, perhaps the first, treatment strategy designed with curative intent (10). Drs. Skipper and Schabel's studies with respect to the first-order kinetic effect of chemotherapeutic agents, as well as other cytokinetic and hematologic studies, were providing increasing biologic insights into the nature of the disease and its perturbation by treatment. As a result of these and other considerations, a four-drug combination of chemotherapeutic agents, Mustargen, Oncovin, methotrexate, and prednisone (MOMP), was constructed for patients with advanced Hodgkin's disease and proved highly efficient in producing complete remission. This was subsequently modified in 1964 by replacing methotrexate with procarbazine (11).

As compared with single-agent treatment, the MOMP/MOPP programs produced very rapid tumor regression, which was often complete and durable (Table 3). Thus, instead of a 0%–20% complete remission rate achieved with single agents, a 60%–70% complete remission rate was achieved with a cure rate of 40%. As three or more independently active agents with qualitatively different dose-limiting toxicity were developed for additional diseases (diffuse histiocytic lymphoma and testicular cancer) (Table 3), similar results were achieved; that is, palliative single drugs were, after appropriate and often extensive clinical investigation, found to be capable of producing curative treatment in combination

TABLE 3

Combination Chemotherapy: Other Curative Regimens

Disease & combination drugs	Dose-limiting toxicity	Full dose %	PR & CR %	CR %
Hodgkin's				
MOPP				
HN_2	Marrow	100	60	10
VCR	Neuropathy	100	55	5
Pred	Corticosteroid	100	35	5
Procarb	Marrow	100	65	15
Total MOPP	—	60 + 100 + 100 + 60		70 (50% cure)
Diffuse Lymphoma				
M-BACOP				
MTX-CF	—	100	55	10
Bleo	Lung	100	40	0
Adria	Marrow	100	65	20
CPA	Marrow	100	65	15
VCR	Neuropathy	100	55	10
Pred	Corticosteroid	100	40	0
Total M-BACOP	—	100 + 100 + 60 + 60 + 100 + 100		80 (ca 50% cure)
Testis Ca				
VBP				
Vinblastine	Marrow	100	50	20
Bleo	Lung	100	40	0
Plat	Kidney	100	65	20
Total VBP	—	100 + 100 + 100		80–90 (70% cure)

HN_2, Mustargen; VCR, vincristine; Pred, prednisone; Procarb, procarbazine; MTX-CF, methotrexate, plus citrovorum factor; Bleo, bleomoycin; Adria, Adriamycin; CPA, cyclophosphamide; Plat, cisplatin.

(12). Further improvements have occurred with the use of crossover treatment designed to minimize the risk of ascendancy of resistant cells, such as MOPP-ABVD for Hodgkin's disease.

A second improvement was the recognition that relapse occurred at pretreatment sites of bulk disease. This was consistent with cytokinetic theory and offered the opportunity of postchemotherapy radiotherapy designed to decrease the risk of relapse. High-dose methotrexate with rescue provided an advantage in treating diffuse histocytic lymphoma because of its independent activity, its lack of myelosuppression, and its penetration into pharmacologic sanctuaries, a significant problem in this disease. It is a greater problem in acute lymphocytic leukemia, and the use of such systemic approaches as high-dose methotrexate is being evaluated in the prophylaxis of the central nervous system. In cancer of the testis, the marked effectiveness of combination chemotherapy is well recognized, and the use of surgery to convert partial responses to complete responses was a major contribution. Similarly, the recognition that only two courses of such treatment could eradicate microscopic disease has major implications.

Adjuvant Chemotherapy. The experience recounted above indicated that curative treatment is possible for certain tumors and that such treatment is far more likely to produce cure when applied to a minimal tumor burden. This is observed in essentially all experimental studies. Accordingly, the use of chemotherapy after control of the primary tumor in patients with various types of solid tumors (so-called "adjuvant chemotherapy") has become an increasingly important strategy; it is well recognized as being important for the treatment of certain childhood solid tumors. Recent well-designed studies indicate that combination chemotherapy, pioneered at an experimental level by Martin, is moderately effective in extending disease-free survival for certain categories of patients with high-risk primary breast cancer and with osteogenic sarcoma. I will not deal with the large number of studies in these areas, except to say that some are unequivocally positive. The principles that are emerging are the need for good models for assessing the biology and perturbation by treatment of micrometastatic disease; increasingly precise discriminants for the presence of micrometastatic disease; the continuing evidence of the superiority of well-constructed combinations over single-agent therapy; the probable, though not conclusive, importance of dose; and the probability that cytoeradication—that is, cure—is either achieved relatively quickly, probably in a few months, or resistant cells have developed, such that time-extended chemotherapy might delay but would not prevent relapse. Thus the future of adjuvant chemotherapy is likely to include emphasis on intensification, new agents, and combinations, in addition to some of the strategies already mentioned.

Neoadjuvant Chemotherapy. Chemotherapy has moved from use in the treatment of advanced refractory, overt disease to use in the treatment of minimal residual disease, and to the adjuvant situation for carcinomas, where chemotherapy is positioned immediately behind surgery and/or radiotherapy.

Neoadjuvant chemotherapy, an old idea whose time has perhaps come, involves chemotherapy as the initial mode of therapy for certain types of solid tumors. The intent of such treatment is to address stage III and IV primary tumors, for which surgery and/or radiotherapy have a low cure rate; reduction of these tumors by neoadjuvant chemotherapy may render local treatment more effective (stage reduction). The second goal is to address micrometastatic disease as early as possible, since experimental studies and modeling, on the basis principally of mutation rates, suggest that the spontaneous development of drug-resistant lines may occur in a relatively short period in micrometastases and, thus, a delay of a month or two might be critical. Neoadjuvant chemotherapy has been employed with preliminary success in head and neck cancer, where 80%–90% of patients had tumor regression, thus an increasing chance for more effective surgery and/or radiotherapy and perhaps for survival; in osteogenic sarcoma, where shrinkage of the primary tumor may improve the opportunity for subamputative local control and particularly may serve as an assay for the effectiveness of the treatment delivered; and in addition, in preliminary studies in such diseases as esophageal carcinoma, cervical cancer, and selected other diseases.

Thus combination chemotherapy, as pioneered by Ezra Greenspan, has become highly effective and curative for many diseases, and indeed essentially all highly effective and curative chemotherapy involves combinations. Increasing clinical investigation and the increasing contributions from our colleagues in the basic sciences relating to such problems as tumor cell heterogeneity, drug resistance, tumor cell differentiation, and novel therapeutic targets, such as those implicit in oncogene products, and immunotoxins undoubtedly will continue to provide accelerating improvement in cancer treatment. At least for the foreseeable future, it is likely that combinations of systemic agents integrated with optimal local treatment will remain the essential strategies in curative treatment (13).

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Prior Tuberculosis in Long-Term Survivors of Breast and Ovarian Cancer from a New York Oncology Practice (1954–1974)

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Abstract

Among 600 patients with disseminated breast and ovarian cancer treated with chemotherapy in a New York-based oncology group from 1954 to 1974, 42 (7%) were long-term (5–20 year) survivors. These survivors showed an unusual incidence of extensive previous tuberculosis, abnormal chest X rays, and positive tuberculin tests; only 25% had negative purified protein derivative (PPD) tests with normal chest X rays. A subset of relatively bulky primary breast cancers with or without positive nodes is known to be associated with higher-than-usual PPD positivity and a relatively indolent clinical course. These retrospective findings suggest that previous tuberculosis may mediate an unusually effective response to chemotherapy.

In a study of the possible influence of tuberculosis on the development of cancer, Pearl (1) 1929 found that active but not inactive tuberculosis was associated with a lower than normal incidence of cancer in 8,600 control-matched autopsies at Johns Hopkins Hospital. Publication of this data caused the Overseers of Harvard Medical School to cancel Pearl's appointment as a senior professor of pathology. A large and conflicting clinical and experimental literature soon evolved regarding the relationship of tuberculosis to cancer. The effect of live bacillus Calmette-Guérin (BCG) on human cancer was reviewed by Bast (2) after Zbar demonstrated the inhibitory action of BCG on guinea pig cancers.

My interest in this subject developed in 1975, when two patients with bulky stage IIIB ovarian carcinoma were found to be apparently cured 9 and 14 years after thiotepa plus methotrexate treatment given in the 1960s. Both had sustained extensive pulmonary and systemic tuberculosis (TBC) as young women 11 and 15 years prior to onset of ovarian cancer. These index cases led to a retrospective analysis (3, 4) of the surviving residue of some 600 heterogeneous stage III–IV patients with breast and ovarian cancer treated at our New York-based oncology group from 1954 to 1974.

Results

An unusual 75% incidence of extensive previous TBC, Ghon foci, apical caps, pulmonary calcifications, and positive tuberculin tests was found among 42 patients unexpectedly surviving 5 to 20 years, either disease-free or with indolent breast or ovarian cancer (Table 1). Only 25% of these 42 long-term survivors were PPD-negative with normal chest x-rays. The denominator needed to precisely interpret these findings was unattainable because many x-rays and records of the 93% of patients who had died had been discarded.

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TABLE 1

Survival 5–20 Years after Stage III–IV Cancer

	Breast cancer*	Ovarian cancer†
Extensive TBC	7	4
Ghon foci or pleural caps	5	4
Tuberculin-positive with calcification	5	1
Tuberculin-positive without calcification	3	1
Tuberculin-negative	5	4
Total	25	14

* Thirteen complete remissions; 12 good or partial indolent remissions (clinically inactive).

† Nine complete remissions; five good partial remissions—one patient died of ovarian recurrence, one of second cancer, and three of subacute myeloid leukemia 5–8 years after remission.

Concomitantly we noted 4 patients with extensive old pulmonary TBC among 7 surviving more than 5 years with metastatic gastrointestinal cancer. Single anecdotal "cured" cases of recurrent invasive bladder cancer and recurrent head and neck cancer were also noted, as well as one case of survival for 21 years with massive retroperitoneal liposarcoma after extensive tuberculosis in 1960. A physician's 86-year-old mother was also observed to survive after three successive visceral primary cancers—independent x-ray–treated ovarian cancer and lung cancer and a resected hypernephroma—all "cured" more than 60 years after a protracted extensive episode of pulmonary TBC.

These retrospective observations of the unusual incidence of previous TBC among survivors of breast and ovarian cancer in New York were highly provocative of the hypothesis discussed below.

Discussion

Factors possibly involved in long-term disease-free survival or apparent cure after disseminated cancer have been intensively investigated in the modern chemotherapy era. The favorable prognostic significance of good immunocompetence has recently been amply documented by survival data in both stage I and stage II breast cancer (5, 6). Better survival associated with Mantoux test positivity in lung cancer (7) and other tumors has also been reported. An "index of immunocompetence" as measured by the response to a panel of PPD plus three to five other cutaneous antigens as well as cellular humoral indices has been proposed as a reliable prognostic guide for clinicians dealing with breast cancer (6). Not only primary-tumor characteristics but also regional metastatic patterns and survival appear related both to PPD response and to previous clinical TBC. It is of some note that the only apparent cure of metastatic large-cell lung cancer in the world literature (8) was treated for an extensive *Mycobacterium kansasii* infection, which developed during the two years the patient was undergoing nitrosourea (lomustine) chemotherapy.

Some clinical oncologists currently use the PPD as part of a panel to simply measure nonspecific delayed cutaneous immunocompetence, although a strong response to PPD often indicates clinically significant previous tuberculosis. The PPD is an index of the varying worldwide epidemiologic exposure to tuberculosis. Normal adult women without breast cancer show a 45% PPD+ rate in New York (9), a 25%–35% rate in Texas (5), a 52% rate in Quebec (10), a 68% rate in Wales (11), a 94% rate in Israel (12), and a 97% rate in Japan (13). The PPD+ rate in primary operable T_1–T_2 breast cancer was recently 44%–45% (Table 2) with or without nodal involvement in New York at Memorial Sloan-Kettering (9) and 41% in Quebec (10). Bolton and co-workers (11) documented in Wales and Krown and co-workers noted without comment in New York (9) that bulky primary breast tumors characteristically are associated with a high PPD positivity rate (69%) (Table 2), in contrast to a lower rate (44%–45%) in small primary tumors regardless of nodal status. Others (11) have also found that locally advanced T_{2-3-4} lesions show a higher rate of positive PPD than normals (Table 2). At M. D. Anderson Hospital in Texas the PPD-positive rate in stage I and early stage II cancer was recently at a 27% level (5). As visceral metastases develop, the rate of positivity declines well below the 40% level (5, 10–13) in North America.

Immunocytologists might deduce that previous TBC acts to recall, facilitate, or trigger favorable macrophage lymphocyte and cellular humoral mechanisms during a chemotherapy-induced release of tumor antigens during the tumor-kill process. It is unlikely that my observations reflect a restoration of PPD responsiveness after a chemotherapy-induced remission in a self-selected population of TBC survivors. Early stage I patients show a lower PPD rate than indolent stage III cancers, and metastatic patterns appear to reflect PPD response and thus past clinical tuberculosis. Moreover, the survival of Japanese women with a 97% PPD rate with stage I cancer

TABLE 2
Percent Incidence of Positive Mantoux or PPD Test in Breast Cancer

	Israel (12)*	Cardiff (11)*	New York (9)*	Quebec (10)*
Controls	94	68	—	52
Perioperative	69	—	44–45	41
T_1N_0	82	59		
T_2N_0	73		45	
$T_{3-4}N_0$	70	65		
T_1N_+	53	57		
T_2N_+	70		44	
$T_{3-4}N_+$	62	53		
Inoperable	60			
Metastatic	35	44		
Skin, soft tissue, nodal			69	
Osseous			65	
Visceral			40	

* Data derived; see reference.

is better than that of American women with comparable stage I disease (14).

A hypothesis could be offered that previous tuberculosis delays but does not prevent the onset of cancer, and thus could lead to an indolent clinical course while creating circumstances for an unusually good chemotherapy response in adults with solid tumors, particularly women aged 40–65. If the concept is valid, then repeated BCG immunization would be warranted in young females, particularly those from high-risk breast cancer families.

However, any enthusiasm for this approach needs to be tempered by the realization that steady weekly BCG immunizations have failed to restore immunocompetence in an elderly (average age 66) predominantly male population in a recent Mayo Clinic study (15) of gastrointestinal cancer, although this study confirmed that those with positive PPD lived longer. Although steady dosages of weekly BCG and BCG products during cancer chemotherapy regimens have generally been futile in several large randomized survival trials, the recent use of a gentle cyclical monthly modulated BCG inoculation has resulted in better survival in stage III ovarian cancer (16), in nodular lymphomas (17), and in females with Duke's C colon cancer (18). Other recent randomized trials with modified BCG schedules in a variety of solid tumors have also been positive.

Comparative data on breast cancer incidence by age are not available on any group of TB patients treated since 1952 when modern chemotherapy first replaced X-ray-controlled chest-collapse procedures in TBC therapy. Thus clinical or epidemiologic data are not now available to prove that exposure, per se, to TBC (or other granulomas, for example histoplasmosis) would inhibit cancer development. Nevertheless, a delay in cancer onset could play a role in creating the flat age-incidence rate at decades from 40 to 70 years in Japanese women (13), as well as the gradual upward slope in European women in contrast to the sharp rise and peak of incidence of high-risk breast cancer in American women at age 45–55 (Clemensen's "hook"). Lack of TBC and other infections should probably be added to nutritional, hormonal, and other environmental factors that may relate to the current epidemic of life-threatening breast cancer so common in the perimenopausal or premenopausal younger female American population.

If prolonged survival from cancer is favorably influenced by prior TBC, especially in the presence of the good chemotherapy responses now obtainable in breast and ovary cancer, then a fresh look should be taken at BCG immunization as a potential prophylaxis. BCG has been used safely worldwide in infants, medical students, and nurses. BCG immunization as a cancer-prevention agent has been tested only as a single dosage in children and infants with leukemia (19) but has never been tested in any comparative study of high-risk women. A controlled randomized trial of repeated BCG vaccination every few years over a 15-year to 20-year period among approximately 20,000 high-risk American women would be required to define any such potential role. A fresh look at BCG stimulation of nonspecific immunocompetence appears warranted on the basis of the clinical findings presented.

Conclusion

Previous tuberculosis in women with breast and ovarian cancer appeared to play a role in unusually good long-term responses to chemotherapy, yielding unexpected long-term disease-free survival or cure.

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General Articles
Specialty Notes

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Colorectal Cancer (Duke's Group B2, C1, C2): Adjuvant Chemotherapy and Toxicity

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In the treatment of colorectal cancer, chemotherapy is being employed more and more often after surgery. Several authors have reported significant improvement of survival and reduced incidence of metastases in large series of patients treated with adjuvant chemotherapy (1–3). The treatment should be planned according to the stage of tumor and the clinical conditions of the patient to obtain the greatest benefits with the least toxicity.

The drugs commonly employed are 5-fluorouracil (5-FU) and MeCCNU. These drugs mostly affect tissues with a high rate of cellular proliferation, as in the gastrointestinal tract, hair bulbs, and bone marrow, producing side effects including alopecia, bone-marrow inhibition, and hepatotoxicity. The liver plays an important role in the metabolism of these drugs; liver toxicity and synergistic actions have been discussed in several papers (4, 5, 7). Careful and regular follow-up is essential for the assessment of drug sensitivity, appearance and severity of side effects, and early detection of metastases (1). Patients on adjuvant chemotherapy for colorectal cancer should be regularly evaluated for Karnofski index (quality of life), myelotoxicity, hepatotoxicity, cardiotoxicity, nephrotoxicity, and presence of metastases.

The purpose of our study was to evaluate efficacy and toxicity of the adjuvant chemotherapy administered according to our protocol:

TREATMENT SCHEME

MeCCNU, 120 mg/m^2, day 1
5-FU, 320 mg/m^2, day 1–2–3–4–5

Repeated for a total amount of 12 times at 37-day intervals.

Materials and Methods

For four years we studied 15 patients with colorectal cancer who had previously undergone radical surgery. All patients were in the B2, C1, C2 group, Duke's classification. Ages ranged from 40 to 72 years; 7 were men, 8 were women. At the beginning of the study, the Karnofski index for all patients was higher than 70. The treatment protocol was as reported above, repeated 12 times with 37-day intervals between treatment periods.

Follow-up studies were performed as follows:

Myelotoxicity: RBC, WBC, Hb, Ht, MCV, MCH, MCHC, and platelets determined during and after each treatment every 7th day for 4 weeks.

Hepatotoxicity: total and fractional bilirubin, SGOT, SGPT, γGT, LDH, total protein, determined at 6-month intervals; liver scan performed at month 6 and 12 and at yearly intervals thereafter.

Cardiotoxicity: ECG at 2-month intervals and chest x-rays every 6 months.

Nephrotoxicity: BUN, creatinine, and creatinine clearance, serum and urine electrolytes, serum uric acid, urinalysis after each treatment (every 4 weeks).

Metastases: chest x-rays, liver scan, and liver sonogram at 6-month intervals.

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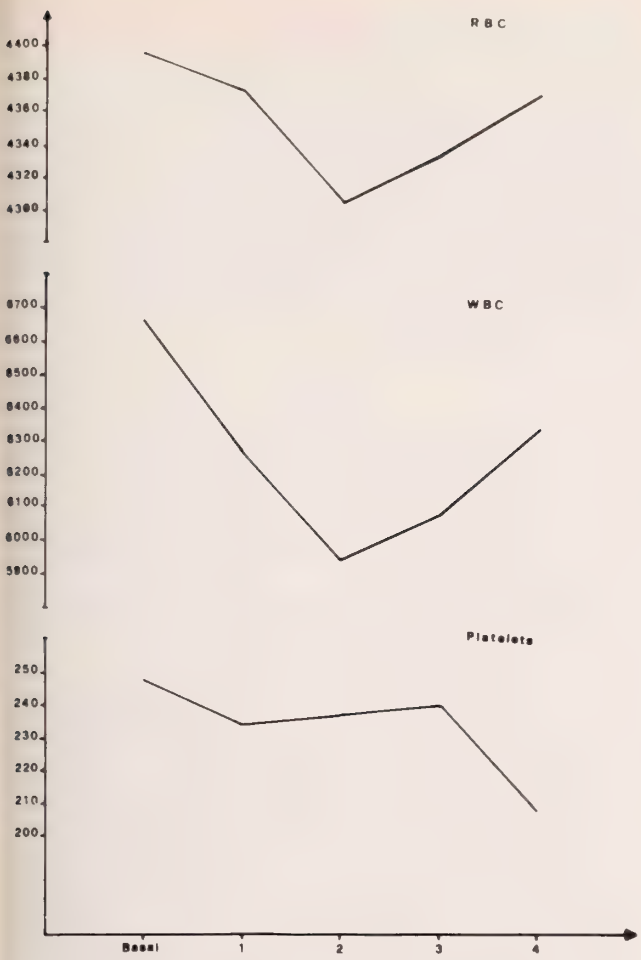

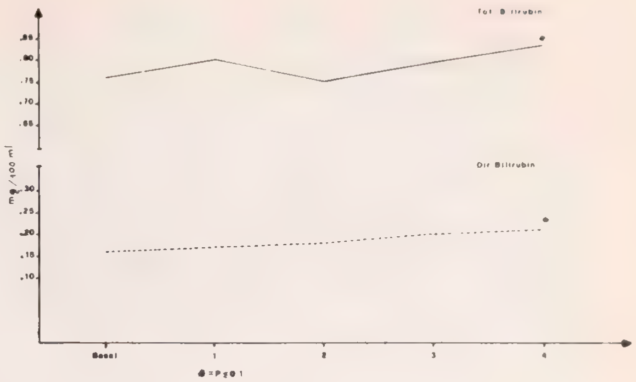

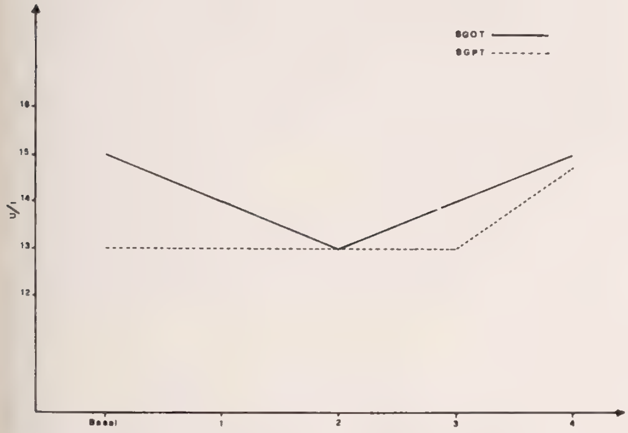

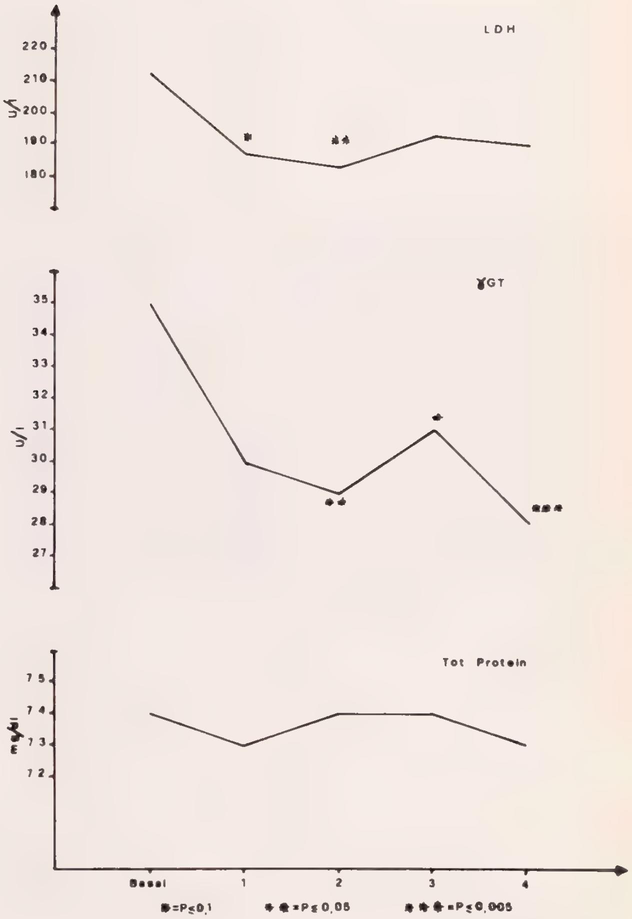

Fig. 1. **Top left** RBC, WBC, and platelets.

Fig. 2. **Top right** Bilirubin; * = $p \leqslant 0.1$.

Fig. 3. **Bottom left** SGOT and SGPT.

Fig. 4. **Bottom right** LDH, γGT, and total protein; * = $p \leqslant 0.1$; ** = $p \leqslant 0.05$; *** = $p \leqslant 0.005$.

Results

The data related to RBC, WBC, platelets, bilirubin, SGOT, SGPT, LDH, γGT and total proteins are plotted in Figs. 1–4. It appears that neither hepatotoxicity nor myelotoxicity were induced at the dosages of 5-FU and MeCCNU administered according to our treatment protocol. In particular, the changes in RBC, WBC, and platelets are not statistically significant.

No statistically significant changes were found in the parameters selected to evaluate for cardiac and renal toxicity.

The incidence of nausea and vomitus were minimal and adequately controlled with antiemetics such as domperidone, which increases the tone of the inferior esophageal sphincter and which favors stomach emptying without affecting gastric secretion.

Throughout our study, no metastases were detected and the Karnofski index was above 70 in all patients at all times.

Discussion

We wish to stress the importance of a careful and regular follow-up to tailor the therapeutic protocol to individual sensitivities to the drugs, as a means to satisfactory therapeutic effect with nil or minimal incidence of the well-known toxic side-effects (6, 7), bone marrow inhibition, immunodepression, changes in the epithelium of the gastrointestinal tract, alopecia, nausea, and vomiting. Most of the chemotherapeutic agents act mainly on rapidly proliferating tissues and each of the agents has a specific organ toxicity.

The protocol we selected produced a significant therapeutic effect, as seen in the clinical course of our patients over the four years of observation and in Karnofski indexes higher than 70 in all patients, together with minimal toxic effect. In fact, no damage could be demonstrated in the organs studied in periodic follow-up.

However, this should not lead us to believe that the described therapeutic scheme is certain in its effectiveness and well tolerated by all post-surgery colorectal cancer patients in Duke's group B2, C1, C2. Strict follow-up and properly selected dosages of drugs remain the mainstay for an adjuvant chemotherapy aimed to ameliorate the quality of life and to prolong life expectancy with the least degree of noxious side effects.

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Solitary Neurofibroma of the Gallbladder: Report of Three Cases and Literature Review

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Abstract

The clinical and pathological features in three cases of neurofibroma of the gallbladder are reported. The lesion appeared in the elderly, unassociated with other stigmata of neurofibromatosis. In two cases it was accompanied by cholecystitis, in the third case the patient had non-Hodgkin's malignant lymphoma.

In the principal reviews of benign tumors and tumorlike lesions of the gallbladder (1–4), solitary neurofibroma has not been documented, except for one instance of a traumatic coexistent neuroma with a suture granuloma (4). Edmondson in his monograph (5) quoted one case of neurinoma of the common bile duct, described by Oden (6), but made no mention of neurofibroma of the gallbladder. Riopelle (7) described neuromatosis of the gallbladder and Yutras (8) concluded that neuromatoses most often associated with adenomyomatosis and cholesterolosis are expressions of what he has called hyperplastic cholecystosis.

We report in this paper the clinical and histopathologic features of three cases of neurofibromatous lesions of the gallbladder, unassociated with either adenomyomatosis or cholesterolosis.

Case Reports

Case 1. A 70-year-old man was admitted to the Department of Surgery of the Rokah Hospital in Tel Aviv with complaints of abdominal pains and weight loss of 10 kg in the last three months. His history included glaucoma of the right eye and left catarectomy. Physical examination revealed moderate hepatomegaly, marked splenomegaly and lymphadenopathy in both axillae and in the left supraclavicular area. Blood pressure was 170/70 mmHg, pulse rate 80/min.

Laboratory investigations revealed anemia (hemoglobin 10 gm/dl, hematocrit 33.8%). The other investigations were within normal limits. Biopsy of an axillary lymph node revealed non-Hodgkin's malignant lymphoma of predominantly large cells, follicular, with diffuse areas.

In a staging laparotomy, enlarged lymph nodes were found near the aorta, the lesser curvature of the stomach, and the hepatoduodenal ligament. Hydrops of the gallbladder was also found and cholecystectomy was performed. The gallbladder showed marked thickening of the wall. Within the cystic duct a small calculus was found.

The postoperative course was unremarkable.

Pathology. Gross examination of the biopsy specimen showed a pale gray nodule, 1 cm in diameter, within the fibrotic wall of the gallbladder. Microscopic examination at lower magnification showed that the nodule was circumscribed, nonencapsulated, lobulated, occupying a major portion of the fibrotic wall (Fig.1). The tumor was composed of elongated spindle cells with indistinct cell membranes, separated by a clear mucinous matrix (Figs. 2, 3). The mucinous matrix stained with alcian blue pH 2.5 for acid mucopolysaccharides. This complex organoid overgrowth of both cells and endoneural matrix is characteristic for neurofibroma.

Case 2. A 65-year-old woman was admitted to the Department of Surgery of the Rokah Hospital

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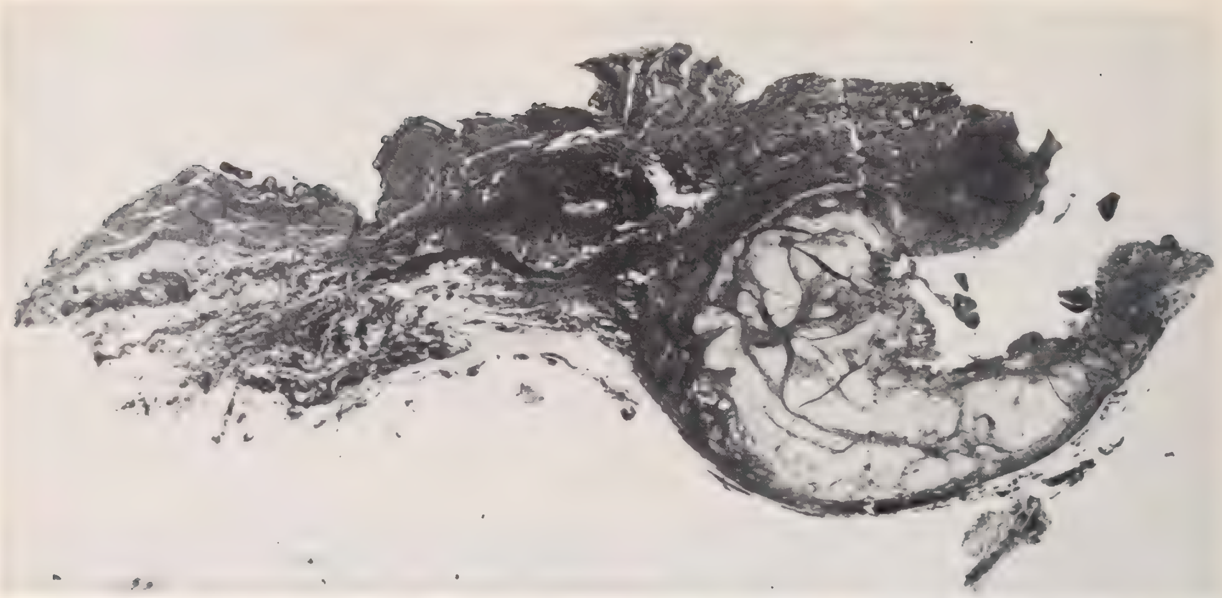

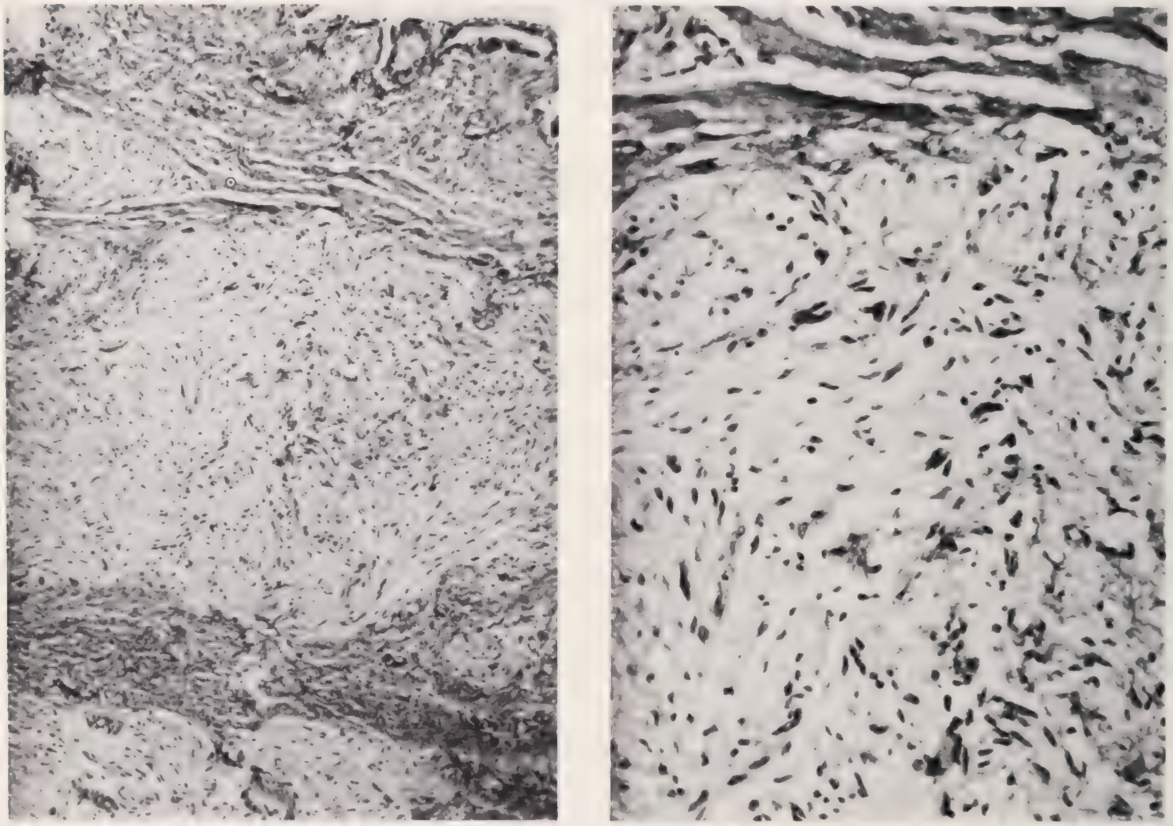

Fig. 1. Top Case 1: Low-power photomicrograph of neurofibroma 1, showing poorly defined lobules occupying almost entire thickness of wall of gallbladder.

Fig. 2. Left Case 1: Higher magnification shows one area of the neurofibroma composed of a mucinous matrix containing spindle cells (Tricrome Masson ×60).

Fig. 3. Right Case 1: Higher magnification showing Schwann cell cylinders widely separated by a mucinous matrix (Hematoxylin and eosin ×200).

in Tel Aviv with complaints of acute abdominal pain in the right upper quadrant, with temperature 38.2°C, nausea, and vomiting. Her history included postprandial dysphagia during the preceding two years.

Intravenous cholecystography did not result in visualization of the gallbladder. Roentgenograms of the chest and abdomen showed nothing remarkable. Results of laboratory investigations were within normal limits, except for serum bilirubin which was 4.6 mg%, and for a while blood counts of 13.500. Blood pressure was 120/80 mmHg and pulse rate 84/min. The patient refused operation and during the following days Gram-negative sepsis and septic shock set in. Serum bilirubin rose to 11 mg%. After treatment with antibiotics and intravenous infusion, cholecystectomy was performed. At operation the gallbladder was shrunken, with marked thickening of the wall. The cystic duct and common bile were dilated, the latter containing some calculi.

Following operation, treatment with antibiotics and plasma was continued. The jaundice decreased gradually and the postoperative course was uneventful.

Pathology. Gross examination of the biopsy specimen showed a grayish white nodule, 1 cm in diameter, within the wall of the gallbladder. Microscopically, the tumor was composed of neurofibromatous tissue, which caused a polipoid protrusion of the inflamed mucosa (Fig. 4). This solitary neurofibroma showed regions resembling a type A schwannoma and other regions with abundant mucoid matrix and a few Schwann cells, suggesting the diagnosis of nerve sheath myxoma, which is considered to be a variant of neurofibroma.

Case 3. A 70-year-old woman was admitted to the Department of Surgery A of Ichilov Hospital in Tel Aviv with complaints of acute abdominal pain in the upper quadrant. Her history included jaundice 10 years before and cataractomy 5 years before. The patient's blood pressure was 140/80 mmHg, her temperature 37.5°C, and her pulse rate 90/min. Sedimentation rate, complete blood count, urine analysis, blood sugar, blood urea, serum electrolytes, serum bilirubin, liver enzymes were all within normal limits. Roentgenograms of the chest and abdomen showed nothing remarkable. Under intravenous cholecystography the gallbladder was not visualized.

A cholecystectomy was performed and revealed a shrunken gallbladder, with a markedly thickened wall, containing two calculi. The patient's postoperative course was benign.

Pathology. Gross examination of the biopsy specimen showed a pale gray nodule, 0.5 cm in diameter, within the wall of the gallbladder. Histologically the nodule was composed of masses of neurofibromatous tissue, closely associated with hypertrophic nerve trunks enveloped in a thick perineurium. Of interest in this case was the localization of the neurofibromatous tissue near the adventitia of an artery (Fig. 5).

Discussion

Nerve hyperplasia and hypertrophy of mild or moderate degree may be observed in surgically removed gallbladder specimens, mainly in cases with thickened, fibrous walls. These enlarged nerve trunks are found in the perimuscular connective tissue and show a regular arrangement. They are different from the masses of neurofibromatous tissue with mucoid matrix, replacing the muscular coat in our cases.

Riopelle has described superficial or mucosal, and deep or adventitial neuromatosis (7), and has pointed out that while the superficial plexus is overdeveloped, the deeply seated one, as well as the connection between the two, remains normal. In our cases, the neurofibromatous tissue replaced locally part or all of the muscular coat, resulting in a nodular structure with marked thickening of the wall. Adenomyomatosis and cholesterolosis, considered by Yutras as frequently associated with neuromatosis in the hy-

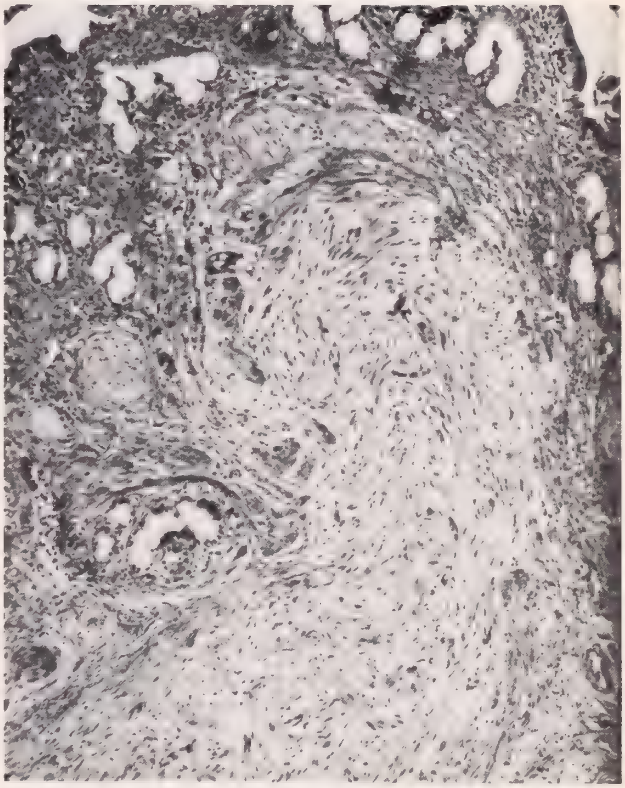

Fig. 4. Case 2: Photomicrograph of neurofibroma causing polypoid protrusion of inflamed mucosa of gallbladder; small nerve twigs are present near the neurofibroma (Hematoxylin and eosin ×200).

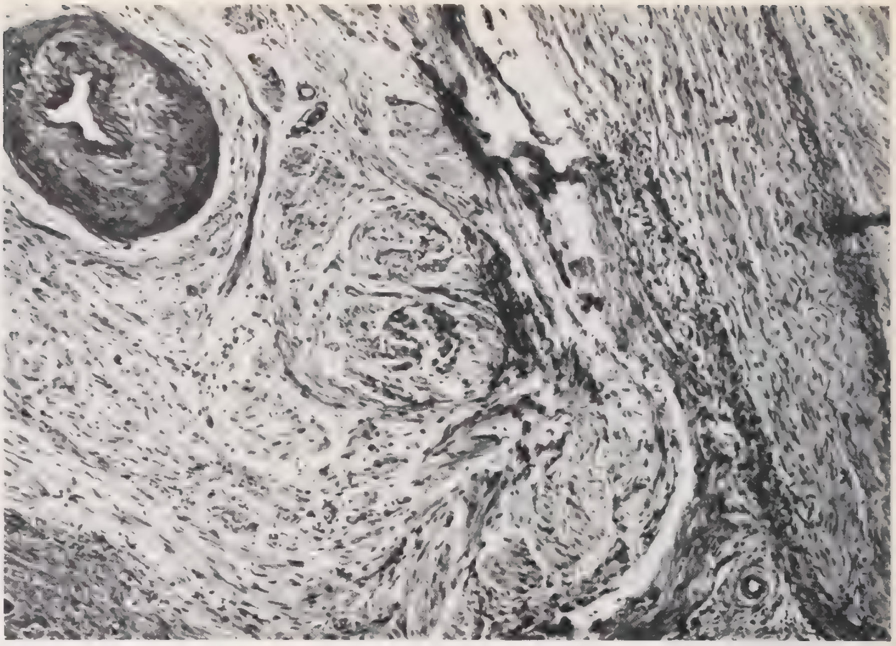

Fig. 5. Case 3: Photomicrograph of neurofibroma in wall of gallbladder near adventitia of an artery; hypertrophied nerve with thick perineurium on right (Hematoxylin and eosin ×200).

perplastic cholecystosis (8), were not found in the present cases. Our findings suggest that we are not dealing with hyperplastia, but with a benign neoplastic process, interpreted as neurofibroma.

Traumatic neuromas were described in the cystic duct stump, after surgical procedures (9–11). In our patients previous surgery had not been performed and the histopathologic features are not similar to amputation neuromas, which retain the nerve-trunk division into fascicles, but these show directional disarray. The lesion in one of our cases (case 3) resembled rather the mucosal neuromas described in the multiple endocrine neoplasia syndromes (12–15). This syndrome was not present in our cases. One case of circumscribed ganglioneuroma arising in the duodenal mucosa was reported by Dahl et al (16) and two examples, both of gastric origin, were reported by Russel and Rubinstein (17). Visceral neurofibroma unassociated with other manifestation of neurofibromatosis is a rare lesion (18). Logan (19) reported one case with neurofibromas of the ileum, cecum, and appendix. Neurofibromas of the gastrointestinal tract unassociated with neurofibromatosis were reported by River et al (20). They were located most often in the ileum, followed by the jejunum, duodenum, and stomach. In the cases associated with neurofibromatosis described by Hochberg et al (21), the most common sites of involvement were jejunum and stomach.

In a case of granular cell tumor of the biliary tract, the periductal tissue showed large, edematous peripheral nerve bundles with occasional disruption of their parallel arrangement and formation of whorls. This lesion was interpreted as a plexiform neurofibroma (22).

In the English-language literature on visceral neurofibromas, including the data from the recent report of Riccardi on neurofibromatosis (23), neurofibroma of the gallbladder was not documented.

Our patients had neither clinical complaints, nor radiologic evidence of visceral multiple neurofibroma of the gastrointestinal tract, nor other neurocutaneous stigmata associated with neurofibromatosis. This lends further support to our conclusion that the lesion described herein is to be considered a solitary neurofibroma of the gallbladder.

Malignant lymphoma and neurofibroma of the gallbladder in the same patient may be coincidental. However, increased nerve-growth-stimulating activity in a patient with malignancy may be suspected.

Wadell et al (24) reported the case of a patient with traumatic neuroma, 27 years after cholecystectomy. This patient had a liposarcoma secreting nerve growth factor, but an association could not be confirmed between liposarcoma secreting nerve growth and the neuroma.

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Environmental Medicine Notes *Alf Fischbein, M.D., editor*

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New Dimensions in Occupational Medicine

Alf Fischbein, M.D.

The successful control of certain infectious diseases that were once a major public health problem is one of the greatest achievements of twentieth century medicine. This success primarily results from the ability to identify and eliminate etiologic agents. Parallel to this development is the recognition that work environments may have a major impact on health, and that a wide spectrum of diseases can result from excessive exposure to agents at the workplace.

Occupational medicine, like most other specialties, is undergoing rapid changes. Those entering the field now will find that new skills are required to master the intricacies of the industrial environment. It is the scientific basis for the development of such skills and their use which will be the main focus for these Notes.

The future practice of occupational medicine will be more concerned with the identification of subtle symptoms, or biochemical perturbations, than with treating the "old" occupational diseases and poisonings. Many of the symptoms related to occupational diseases are nonspecific, requiring a high index of suspicion on the physician's part: he or she must learn how to recognize the potential risks in work environments. Thus, familiarity with the industrial environment is essential for the early detection, diagnosis, and prevention of occupational diseases. Knowledge of industrial hygiene will become an ever more important clinical tool for the occupational health physician. A well-characterized work environment—albeit outside the physician's responsibility—is also required for the establishment of dose-response relationships, which are essential in developing standards for exposure limits and for medical surveillance.

The determination of safe levels of exposure will become a crucial issue, and the occupational physician, responsible for the health of workers, will be obliged to make decisions regarding safety of individual workers. Therefore, the moral and ethical responsibilities of the occupational physician go beyond traditional concepts. The matter becomes even more complex: for some industrial compounds, the question arises whether a safe exposure level exists at all! This is a particular problem with carcinogenic compounds. For most of these compounds, safe exposure levels for humans have not been established, and extrapolation is made from experimental data for standard-setting, for assessment of risk, and for clinical judgments in occupational medicine: a good example of a medical-ethical dilemma.

Although we are still in the embryonic stage in clarifying the causes of human cancers, it is evident that occupational, environmental, and lifestyle factors play an important role. How "new" this phenomenon is can be disputed. One of the earliest reports on occupationally related cancer, describing the increased risk of scrotal cancer in chimneysweeps, was published in 1775. It was at the end of the nineteenth century that the association between bladder cancer and exposure to aromatic amines was recognized among dye workers, and the risk of increased lung cancer was discovered among uranium miners in Schneeberg in central Europe. Suspicion that inhalation of asbestos fibers can cause lung cancer was published in case reports in the 1930s, and during the subsequent three decades the cancer-causing potential of asbestos was verified in epidemiologic studies.

In the 1980s, other chemicals common in the work environment, such as manmade mineral fibers, formaldehyde, and methylene chloride, have come under close scrutiny because of their carcinogenic potential. For most compounds, the initial information about carcinogenicity is obtained in experimental studies. Assessment of human risk factors is complex and confirmation must often await epidemiologic evidence.

The characteristically lengthy period of clinical latency between onset of exposure and clinical manifestation of occupational cancers is three or four decades. These diseases are detected in retrospect; early detection of occupational cancers by human studies are almost impossible. The biological processes operating during this latency period have not been well characterized, and unless we achieve a better understanding of them, the outlook is gloomy for those workers already exposed and, therefore, at high risk for developing occupational cancers. The identification of persons at high neoplastic risk and the development of methods for cancer prevention are urgent research needs. Among the approaches which have received increased attention in this context are measurement of immune dysfunction among persons with a history of exposure to agents with proven or suspect carcinogenic effects in humans, and the potential usefulness of certain tumor markers—modified nucleosides—in identifying persons at high neoplastic risk rather than patients with clinically evident malignancies.

A brief introduction to current concepts in nucleoside research and the interaction of those concepts with the concerns of occupational medicine constitutes the first of these Environmental Medicine Notes.

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Modified Nucleosides and Early Detection of Occupational Cancer: A Challenge for the Future

ALF FISCHBEIN, M.D., OPENDRA K. SHARMA, PH.D., AND ERNEST BOREK, PH.D., M.D. (HON. C.)

The hope of finding unique metabolic products or components of malignant cells in body fluids which could serve as early indicators of cancer has posed a great challenge to the medical community for several decades. The term "tumor marker" has been defined as a product circulating in body fluids and accurately reflecting the presence of a malignant process (1).

Properties of tumor markers essential for usefulness in the early detection of cancer include the appearance of the substance in the blood or other body fluids, specificity for cancer and tissue, and correlation between levels of tumor marker and tumor burden, as well as high reliability of the assay and applicability to screening of large populations (2).

A great number of such biochemical indicators aimed at providing the clinician with a sensitive diagnostic tool have been reported, but their usefulness has been limited by low sensitivity, low specificity, or both (3). Some tumor markers have been useful in monitoring response to therapy, but to our knowledge none have been reported to be efficient indicators of occult malignancy at a preclinical stage.

Biochemically, tumor markers are essentially either hormones, proteins, or metabolites of nucleic acids. The small number of malignant tumors associated with elevated levels of hormones obviously limits the use of hormones as "universal" tumor markers. Attempts to identify tumor-specific proteins as "ideal" tumor markers have met with only limited success, primarily because of the difficulty in identifying, among the thousands of different proteins synthesized by both normal and malignant cells, a particular protein that can be causally related to the malignant process. It has been suggested that a universal tumor marker should be sought in a biological system which is aberrant in malignant tissue in general (4).

Modified Nucleosides as a Marker. Transfer RNA (tRNA), a cardinal component of genetic expression in every cell, is a most complex biomacromolecule in both structure and function. In addition to the four major bases—adenine, cytosine, guanine, and uracil—proper tRNA function requires that some of these bases undergo modifications. The most common modification is methylation, which requires different methyltransferases. The impetus to study tRNA methyltransferases in tumor tissue was provided by Magee (5). The enzymes that methylate tRNA in malignant tumor tissue differ both quantitatively and qualitatively from those that operate in normal tissues. The tRNA methyltransferases in malignant tissue are abnormally hyperactive, and the tRNA turnover is very high (6, 7).

The experimental and clinical evidence for these biochemical events is that tumor-bearing animals and persons with cancer excrete in their urine elevated levels of such modified purines, pyrimidines and their ribosides, known as nucleosides (8, 9). Isotope studies have demonstrated that some nucleosides originate exclusively from tRNA breakdown and not from tissue degradation (7).

Thus it seems that the measurement of excre-

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tion of modified nucleosides is a feasible way of identifying the presence of different malignancies. Moreover, it has been demonstrated that elevated marker levels return to normal after effective chemotherapy of at least a few neoplasms, including Burkitt's lymphoma, acute T-cell lymphocytic leukemia in children, Hodgkin's lymphoma, and choriocarcinoma (10, 11). There are also indications that a relationship exists between nucleoside excretion levels and the clinical stage of small-cell carcinoma of the lung (12). Similar results have been found with histiocytic lymphoma, lymphocytic lymphoma, and Hodgkin's disease.

The analytical methods for the quantification of modified nucleosides using high-performance liquid chromatography have been described in detail (13) and are currently performed in a number of laboratories throughout the world.

Modified Nucleosides and Occupational Cancers. It has been recognized that some cancers develop as a result of the influence of extrinsic or environmental factors (14). Occupational exposures to carcinogenic compounds represent subgroups of such causative factors. It is possible that the potential for cancer prevention is particularly great for those malignant diseases in which extrinsic factors are of greatest importance. Adding this to the indirect influence by extrinsic factors on other factors which increase the risk of neoplasms of apparently intrinsic origin, it would seem that a great proportion of human cancer is potentially preventable.

Therefore, there is an urgent need to explore new diagnostic approaches with potential for detecting pathophysiological changes at a preclinical stage, so that early diagnosis can be achieved and curative treatment performed. Of even greater importance would be the possibility of identifying individuals who are at particularly high risk of developing cancer (15).

Asbestos-Related Neoplastic Diseases. Asbestos-associated diseases are an occupational and environmental health problem of great magnitude in the United States. Perhaps of greatest concern is the association between asbestos exposure and increased risk of lung cancer, malignant pleural and peritoneal mesothelioma, and other types of cancer such as colorectal tumors; such an association has been documented in mortality studies of large asbestos-exposed populations (16).

The long period of clinical latency between the onset of exposure and the clinical manifestations of asbestos-associated malignant disease is characteristic of occupational cancer in general (17). This is of particular interest in the context of studying the relationship between a pattern of urinary nucleoside excretion and the development of asbestos-related cancer. Little information is available concerning the biological and biochemical events that occur during the period of clinical latency, which is usually 20–30 years for lung cancer and often longer for mesothelioma. From a clinical viewpoint, early diagnosis of mesothelioma and other asbestos-related neoplasms is uncommon, and the potential for curative therapy is severely limited.

Nucleosides in Urine. Feasibility studies have explored the pattern of urinary nucleoside excretion in a population of asbestos-insulation workers with a long history of occupational exposure to asbestos, and without detected malignancies, but at high risk of developing cancer.

One feasibility study addressed the question whether patients with asbestos-associated malignant mesothelioma excrete elevated levels of modified nucleosides in their urine. In this and subsequent studies the following compounds were measured: pseudouridine (ψ), 1-methylguanosine ($m'A$), 2-pyridone-5-carboxamide-N′-ribofuranoside (PCNR), 1-methylinosine ($m'I$), 1-methylguanosine ($m'G$), N_2-methylguanosine (m_2G), M_2M_2-dimethylguanosine (m_2^2G), N_4-acetylcytidine (ac_4C), and β-aminoisobutyric acid (BAIB). Eight patients with mesothelioma were studied, and all patients showed elevated levels of several nucleosides (18). We have confirmed our initial observation in an additional 7 patients with malignant mesothelioma.

A second study was conducted with a group of 47 asbestos insulation workers, for whom 30 years or more had passed since the onset of asbestos exposure, in almost every case, but who did not have any clinical signs of malignant disease. The study population exhibited significantly higher levels on 7 of the investigated nucleosides when compared to a control group. Moreover, 27 (57%) had three or more nucleosides elevated, indicating a markedly abnormal excretion profile (19).

We have also applied discriminant analysis as an effective multivariate statistical tool on the same study and control populations, and have shown that it was possible to predict accurately from the controls (20) the group of asbestos insulation workers at high neoplastic risk. It should be emphasized, however, that the elevations of modified nucleosides in the asbestos-insulation workers at high neoplastic risk were less than the elevations noted among the patients with mesothelioma, and that most of the examined individuals had evidence of asbestosis because of their long history of excessive exposure to airborne asbestos.

Comment. Much evidence has been accumulated indicating that patients with certain cancers have altered urinary excretion patterns of modified tRNA breakdown products, and that successful therapeutic intervention can normalize the level of excretion. We have initiated studies to assess the possibility of extending the usefulness of measuring urinary nucleoside markers and to adapt such determinations to a clinical tool for the identification of individuals at high neoplastic risk. Having demonstrated that patients with asbestos-related malignant pleural mesothelioma exhibit abnormal urinary levels of modified nucleosides, we found a high prevalence of similar abnormalities in a population of asbestos-insulation workers with a long history of asbestos exposure who, at the time of examination, did not have clinical evidence of neoplasia.

A recent experimental study has shown increased excretion of pseudouridine and hypoxanthine in nude mice transplanted with mesothelioma (21). In that study the excretion of pseudouridine appears to have been related to the growth of the mesothelioma, and the increased excretion commenced at a time when the tumor was just measurable. Other experimental studies have provided support for the notion that increased excretion of modified nucleosides may precede tumor diagnosis (22, 23).

Our findings of elevated urinary levels of modified tRNA breakdown products in asbestos-insulation workers at high neoplastic risk is of interest in light of these experimental studies. Although an increased turnover rate of tRNA has been reported in tumors (7), which we believe is the principal reason for elevated excretion levels, others have suggested that the increased excretion rate in tumor-bearing individuals is an expression of an altered general metabolism of the whole organism preceding and accompanying tumor growth (22). Support for this hypothesis has been provided by studies showing an altered pattern of tRNA isoacceptors not only in the tRNA of tumor cells but also at distant sites (23).

The results of our initial investigations of asbestos-insulation workers can provide a foundation for future studies aimed at assessing the *predictive* diagnostic value of measuring modified nucleosides. This question is currently being addressed by prospective observation of a large population of asbestos-insulation workers.

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Gastroenterology Notes

David B. Sachar, M.D., editor

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In the first column of this series, September 1984, Dr. Lawrence B. Cohen discussed the clinical applications of modern manometric techniques for the evaluation and treatment of disorders of gastrointestinal motility. Now, in the present article, Dr. Gerald Friedman describes some new gastrointestinal drugs currently under clinical investigation in the United States. These agents may provide some new weapons against a variety of stubborn and problematic digestive diseases.—DBS

New Drugs in Gastroenterology

Gerald Friedman, M.D., Ph.D.

This article describes four selected pharmacologic agents currently under clinical investigation in the United States. Each of these agents is representative of a group of drugs that may fill a specific therapeutic gap in the management of various gastrointestinal disorders. The data contained herein do not represent an exhaustive review of either the drugs or the diseases for which they may prove useful, but rather provide a glimpse into some future therapeutic possibilities. The published literature has been surveyed, as have the investigational brochures, provided by courtesy of a number of pharmaceutical companies involved in investigations of these agents.

1. A Nonabsorbable Steroid for Intrarectal Treatment of Distal Colitis

Drug: Tixocortol pivalate (preg-4-ene-21-thiol-11B,17-dihydroxy-21-pivalate), Sandoz.

Indications. Intrarectal administration of a nonglucocorticoid, nonmineralocorticoid steroid with local and topical antiinflammatory activity employed in the treatment of proctitis, proctosigmoiditis, and left-sided ulcerative colitis.

Background. Approximately 60% of all cases of nonspecific ulcerative colitis involve the rectum, sigmoid, or descending colon. Clinically, these cases are characterized by diarrhea, rectal bleeding, and abdominal cramps, usually with the absence of fever, leukocytosis, or extracolonic manifestations of inflammatory bowel disease. Many of these patients are treated as outpatients. Heretofore, treatment has consisted of a hydrocortisone suspension of 100 mg in 60 ml of diluent instilled nightly or twice daily, frequently achieving a beneficial effect. The duration of these instillations may be 1 to 4 weeks depending on the clinical response. In addition, many physicians add sulfasalazine orally in a dosage of 2 to 4 gm daily. The major drawbacks of rectally instilled absorbable steroids are the side effects, which are the same as for orally administered steroids. In fact, 50%–75% of rectally administered hydrocortisone is absorbed, depending on the total duration of retention of the agent (1) (that is, the longer the duration of retention, the greater the degree of absorption).

In selecting therapeutic agents for these forms of inflammatory bowel disease, it should be remembered that the recurrence rate of proctitis, proctosigmoiditis, and left-sided ulcerative colitis is high, ranging to about 4 times yearly. The frequent exposure of these patients to rectally absorbed steroids is therapeutically undesirable. In addition, a significant number of patients with left-sided disease are refractory to all current forms of therapy, including the combination of hydrocortisone enemas and sulfasalazine.

Clinical Experience. Tixocortol pivalate is a nonglucocorticoid, nonmineralocorticoid steroid with local and topical antiinflammatory activity (2). Its local antiinflammatory activity is at least equivalent to or greater than that of hydrocortisone acetate. Local or topical administration of tixocortol pivalate in animals exerts almost no systemic activity. A recent publication by Dr. T.

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Larochelle and associates at the University of Montreal (3) evaluated a group of 18 normal subjects to determine whether tixocortol pivalate exerted any systemic glucocorticoid activity after a single oral or intrarectal dosage or after short-term dosing by the intranasal route. The effects of tixocortol pivalate were compared to those of oral dexamethasone and intrarectal betamethasone 21-phosphate. By the three routes, Tixocortol did not induce any change in plasma cortisol, leukocyte counts, blood glucose, or 24-hr urinary excretion of sodium and potassium. There were such changes after dexamethasone and betamethasone. These authors concluded that tixocortol pivalate administered for short periods by nonparenteral routes did not induce a measurable systemic glucocorticoid effect.

Under the name Rectovalone, a rectal suspension of tixocortol pivalate has been used in the treatment of left-sided ulcerative proctitis. Two multicentered clinical trials were conducted in France in an effort to determine the activity of tixocortol pivalate in the treatment of acute attacks of ulcerative colitis. The first of these studies involved a randomized trial comparing tixocortol pivalate and betamethasone in the treatment of acute attacks of ulcerative colitis in 66 patients. Both substances were administered rectally in a volume of 100 ml nightly for 20 nights. The patients treated with betamethasone received 5 mg of active medication, and those treated with tixocortol received 250 mg in each enema. These doses are equivalent to between 200 and 400 mg of hydrocortisone. Symptomatic improvement was demonstrated in 80% of patients on tixocortol pivalate and 79% of patients on betamethasone, resulting in reduction in bleeding and diarrhea, absence of mucorrhea, and induction of clinical well-being. Absence of blood in the stool was noted in 86% of the patients on tixocortol and 55% of the patients on betamethasone. Stool frequency was reduced in 65% of patients on tixocortol and 50% of patients on betamethasone. A reduction in cortisolemia occurred in 9% of patients on tixocortol and 67% of patients on betamethasone.

In the United States, Sandoz, Inc., has completed two randomized double-blind clinical trials comparing the efficacy and safety of tixocortol pivalate and hydrocortisone suspension in the treatment of patients with ulcerative colitis. A third trial using similar criteria is nearing completion. In addition, a dose-response trial employing three separate dose levels of tixocortol pivalate is being performed.

Both tixocortol pivalate and hydrocortisone enemas appear to be effective in reducing inflammatory bowel activity and inducing healing.

Tixocortol pivalate has the potential advantage of the absence of significant side effects, particularly those associated with adverse glucocorticoid and mineralocorticoid states. A flexible dose may be employed without concern for undesirable side effects. A nonglucocorticoid, nonmineralocorticoid steroid compound having comparable or greater antiinflammatory activity without producing adrenal suppression or steroid-induced side effects should prove to be a major advance in topical therapy of certain forms of inflammatory bowel disease.

2. A Synthetic Prostaglandin Analog for Treatment and Prevention of Peptic Ulcer Disease

Drug: Trimoprostil (RO-21-6937), Roche. RO-21-6937 is 11R,16,16-trimethyl-11-desoxy-prostaglandin E_2, a synthetic prostanoid.

Indications. Treatment of gastric and duodenal ulcers and hemorrhagic gastritis.

Background. Prostaglandins are a family of long-chain oxygenated fatty acids occurring naturally in mammalian tissue. More than two decades of research has resulted in the identification of over 20 natural prostaglandins and the synthesis of many analogs. The gastrointestinal tract contains large amounts of prostaglandins. The major effects of prostaglandins on the gastrointestinal tract appear to be on acid secretory activity, gastrointestinal motor function, and cytoprotection of gastrointestinal epithelium (4–8). Several methyl analogs of PGE_2, when orally administered, have been shown to inhibit basal and stimulated gastric acid secretion in humans. Methyl analogs of PGE_2 accelerate the healing of gastric and duodenal ulcers in humans (9, 10). The new analogs of prostaglandins appear to have greater specificity of action accompanied by fewer side effects.

Research activity in the treatment of peptic ulcer disease, stimulated by the introduction of cimetidine in 1977, the later introduction of ranitidine, as well as the reinvestigation of the efficacy of antacid therapy, has demonstrated that accelerated healing of duodenal and gastric ulcers may be accomplished. These agents have been less effective in the therapy of acute upper gastrointestinal tract bleeding, particularly when the bleeding is associated with acute hemorrhagic gastritis. The prostaglandins may add another dimension to the treatment of hemorrhagic gastritis by providing a unique cytoprotective effect, thereby reducing bleeding and promoting healing. Indeed, a disassociation of the effects of reduced gastric acid secretion and the healing of acute hemorrhagic gastritis has been demonstrated. It appears that a lower dose of prostaglandins that does not inhibit acid secretory activity may in fact have a significant cytoprotective effect.

Clinical Experience. Trimoprostil has unique pharmacologic properties affecting many of the postulated pathogenetic factors in the genesis of peptic ulcer disease (11). Trimoprostil produces a reduction in gastric acidity, inhibition of pepsin secretion, and enhancement of mucoprotein secretion and synthesis, as well as a cytoprotective effect. The multifactorial pharmacologic activity of this compound may offer advantages over other antiulcer drugs that affect only one of the factors considered to be implicated in the pathogenesis of peptic ulcer disease. International research activity covering the pharmacologic effects of this agent have been carried out in the United States, Switzerland, and Japan.

A number of preclinical studies indicative of the pharmacologic potential of trimoprostil have been performed. Trimoprostil was demonstrated to be a potent inhibitor of basal gastric secretion in the conscious rat with an acute gastric fistula. Under these circumstances the compound was more potent than PGE_2 and much more potent than cimetidine. Under conditions of submaximal histamine stimulation in two animal models, trimoprostil inhibited gastric secretion. Under conditions of maximal histamine stimulation, the compound inhibited both pepsin concentration and output in dogs prepared with Heidenhain pouches. In rats and guinea pigs, trimoprostil prevented experimental ulceration produced by pyloric ligation, stress from immersion or forced swimming, administration of Indocin, or repeated administration of carbachol and 4-methyl histamine.

In summary, animal studies have revealed that trimoprostil causes reduction in gastric acidity and pepsin secretion, enhances mucoprotein synthesis and secretion, prevents experimentally induced ulcers, and protects the gastric mucosa against micro bleeding induced by aspirin. Thirteen-week toxicity studies of rats and dogs revealed neither clinical nor laboratory evidence of drug intolerance.

Trimoprostil has been given orally to more than 200 normal healthy volunteers in an effort to determine tolerance, pharmacokinetics, and antisecretory and cytoprotective activity. Pharmacokinetic studies on six normal male volunteers using doses of 750 μg qid for 14 days revealed that the drug is rapidly absorbed, reaching peak blood levels 20–40 min after oral administration. The concentrations of the drug noted on days 1 and 14 were similar; thus no evidence of accumulation of the agent was found. The mean half-life appeared to be 45 min on day 1 and on day 14. When the drug was administered with food, there appeared to be evidence of delayed absorption with the postprandial dosage.

A study of the cytoprotective activity of trimoprostil in aspirin-induced fecal blood loss using the ^{51}Cr-labeled red blood cell procedure revealed that mean aspirin-induced blood loss using a dose of 650 mg of aspirin four times a day in placebo patients was approximately 4.40 ml/24 hr. Administration of 2, 4, and 6 mg/day of trimoprostil revealed that the active treatment group had significantly less blood loss than the placebo group. There was no obvious dose-response relationship at these three drug levels.

On the basis of the studies noted above and other data, the effects of trimoprostil are being tested in patients with gastric ulcer. The study includes an 8-week randomized double-blind multicenter study comparing the effects of trimoprostil and placebo on the healing and symptomatology of benign gastric ulcer disease.

In summary, pending further clinical trials at this time, it seems reasonable to suggest that the rate of healing of duodenal ulcers appears to be more rapid with H_2 antagonists than with the prostaglandins. The suppression of acid secretory output by each of these two groups of agents appears consistent with these findings. Previously published clinical studies with the H_2 antagonists indicate statistically significant rates of healing at 2 weeks as well as at 4 and 6 weeks. It is likely that low-dose prostaglandins may find their greatest use in the treatment of gastric ulcer and acute hemorrhagic gastritis, in large part owing to the implied cytoprotective effects of the agents.

3. A Dopamine Receptor Blocker with Gastroprokinetic and Antiemetic Properties

Drug: Domperidone, 5-chloro-1-1-3-(2,3-dihydro-2-oxo-1 H-benzimidazol-1-yl) propyl-4-piperidinyl-1,3-dihydro-2 H-benzimidazole-2-one, Janssen, a benzimidazole derivative.

Indications. A gastroprokinetic drug with potent antiemetic properties currently under clinical investigation in the United States.

Background. Gastroprokinetic agents (the prototype is metoclopramide) have been used clinically for the treatment of gastroesophageal reflux and delayed gastric emptying and as antiemetics. These agents are of particular value in the treatment of transient delayed gastric emptying of a functional nature such as seen in postoperative ileus, diabetic gastroparesis, gastric ulcer disease, and certain connective-tissue disorders. The drugs also reduce gastroesophageal reflux by promoting gastric emptying and raising lower esophageal sphincter pressure. Domperidone appears to have certain advantages over metoclopramide in that it is better tolerated by infants and children and can be used on parkinsonism patients. Domperidone does not cross the blood-brain barrier and, as a result, is associated with fewer sedative side effects.

Clinical Experience. Domperidone was first synthesized in 1974 in the Belgian laboratories of Janssen Pharmaceutica (12). The drug possesses significant blocking actions against peripheral dopamine receptors. Domperidone is available in Europe, where it has been extensively used for the conditions noted above. The drug is well absorbed when given intramuscularly, intravenously, orally, or rectally and is extensively metabolized by the liver. It is excreted mainly as inactive metabolites in the bile and has a half-life of about 8 hr. Bioavailability studies reveal that domperidone achieves peak plasma levels within 15–30 min after intramuscular and oral administration and 1–2 hr after rectal administration. Large numbers of patients treated chronically with domperidone revealed no hematologic or biochemic abnormalities. No extrapyramidal side effects were noted even at higher doses (13).

Intraluminal manometric studies have shown that domperidone increases lower esophageal sphincter pressure. The drug increases the amplitude of esophageal and duodenal and peristaltic activity but has no effect on gastric acid secretion or endogenous gastrin release. Human pharmacologic studies demonstrated that the gastric emptying rate in healthy volunteers was enhanced after an intravenous dose of 5 mg of the agent. Gastroscopic evaluations reveal that it produces an increase in maximal pyloric diameter without affecting motility or contractility.

These results suggest that the agent may be useful in the treatment of gastroesophageal and gastroduodenal reflux. Its major value appears to be as an antiemetic. It is particularly effective in combination with cytostatic therapy in cancer chemotherapy. It has been demonstrably effective in the treatment of cerebral vomiting and nausea, in the treatment of nausea and vomiting during dysmenorrhea, in hemodialysis-associated vomiting, and as a premedication for esophagogastroscopy.

Additional motor studies of the stomach and small bowel reveal that intravenous or oral domperidone promotes antral peristalsis and gastric emptying compared to placebo. The results of these and similar studies suggest that domperidone improves the motor function of the proximal gastrointestinal tract and synchronizes motor function owing to its protracted activity.

The mechanisms of action of the available gastroprokinetic drugs differ. Bethanechol acts cholinergically, whereas metoclopramide has antidopaminergic central and peripheral actions. Domperidone, on the other hand, has antidopaminergic actions peripherally and only in that part of the chemoreceptor trigger zone which is partially outside of the blood-brain barrier. The lack of significant central nervous system side effects may prove to be advantageous in infants and children, providing more flexible dosage, negligible sedation, and greater utility when used on patients with parkinsonism. Its pronounced antiemetic properties should be useful as a companion agent in cancer chemotherapy. A flexible dosage selection is enhanced by the availability of parenteral, oral, and suppository forms of the medication.

4. An Alpha-2 Adrenergic Agonist With Antidiarrheal Activity

Drug: Lidamidine hydrochloride (WHR-1142A, Rorer) is 1-(2,6-dimethylphenyl-3-methylamidino area hydrochloride), an alpha-2 agonist.

Indications. A chemically new and pharmacologically unique antidiarrheal agent that appears to be free of narcotic and anticholinergic activity (14).

Background. Over the past 10 or more years, evidence has accumulated that the primary pathophysiologic mechanism of diarrhea is an abnormality of intestinal water and electrolyte transport. The question whether muscle or mucosa is the primary site of action of antidiarrheal agents remains unsolved. Advocates of the muscle site of antidiarrheal action point to the delayed intestinal transit associated with nonpropulsive muscle activity. Some antidiarrheal drugs appear to cause increased rhythmic activity of intestinal circular muscle while inhibiting the contractility of gut longitudinal muscle. The fecal stream is consequently held in the intestine, allowing time and the mucosa to accomplish more efficient absorption of fluid and electrolytes. Other investigators have presented evidence for an effect of endogenous, natural, and synthetic opiates on water and electrolyte transport by the intestine. It is likely that both of these mechanisms may be operative, acting in concert, in producing the overall antidiarrheal effects.

In 1973 Field and McColl (15) demonstrated that alpha-2 adrenergic agonists stimulate sodium and chloride absorption in the intestine. This finding suggested that the compounds could be useful as antidiarrheal agents. A number of investigators (16, 17) found that ion transport in the rabbit ileum was mediated by alpha-2 adrenergic receptors. A prototype of these agents, clonidine, was shown to stimulate water and electrolyte absorption in humans, thus inhibiting diarrhea (18). In order to circumvent the cardiovascular and central nervous system side effects, newer analogs have been developed. Dharmsathaphorn et al (19) have studied the structure, activity, and relationships of a number of imidazoline derivatives, compounds with structures similar to that of clonidine. These investigators have indicated that it may be possible to develop an alpha-2 adrenergic agonist with specificity for the gut intestinal receptor, which in addition will be unable to cross the blood-brain barrier, thus minimizing central nervous system effects.

Clinical Experience. Lidamidine hydrochloride (lidamidine) inhibits diarrhea in animals, specifically the diarrheal episodes induced by PGE_2, castor oil, carbachol, and serotonin (20, 21). Antidiarrheal activity under these circumstances appears to be greater than that of loperamide and diphenoxylate. Lidamidine is rapidly and quantitatively absorbed from the gastrointestinal tract in the rat and monkey after a single dose. Peak plasma levels occur within 30 min, and the compound is found in both plasma and blood cellular components. The half-life of the parent compound is one-half hour in the rat and 1 hr in the monkey. Lidamidine is quantitatively absorbed in humans, reaching peak plasma levels between 1 and 4 hr after ingestion. Excretion appears to be primarily renal and accounts for a mean elimination of 98% of the administered dose. Most of the urinary elimination occurs within 0–48 hr and is complete at 96 hr after ingestion. Lidamidine is excreted primarily as the intact compound.

Safety studies using a double-blind placebo control employing multiple oral-dose levels of lidamidine reveal that the dose levels between 20 mg and 200 mg are tolerated without any consistent abnormalities. At lower doses the drug reveals no clinically significant influence on blood pressure or pulse rate. At very high doses, greater than 160 mg, a trend toward orthostatic hypotension is noted. Major side effects of lidamidine occur at high doses and include hypotension and hyperglycemia, possibly related to alpha-2 agonist inhibitory effects on the central nervous system and on receptors inhibiting insulin release.

Clinical studies with lidamidine hydrochloride in the United States have been conducted on more than 300 patients with acute nonspecific diarrhea. These double-blind placebo-controlled studies employed two 4-mg lidamidine capsules or matching placebo, and one capsule (2 mg lidamidine or placebo) after each subsequent bowel movement. Other studies compared placebo with a fixed dosage, twice a day regimen. In both these groups the mean number of stools for the first 24 hr of dosing was less in the lidamidine-treated group than in the placebo group. Side effects were minimal and not statistically significantly different between lidamidine and placebo groups. Mild abdominal pain, dizziness, and dry mouth accounted for most of the reactions reported. Additional multicenter double-blind, parallel controlled studies are in progress comparing lidamidine and placebo in the treatment of acute nonspecific diarrhea.

Other studies on patients with chronic diarrhea include patients with short-bowel syndrome, inflammatory bowel disease, pancreatic disease, and irritable bowel syndrome. In these various studies physicians rated the drug effective or possibly effective in approximately 72% and ineffective in about 28% of patients. Overall adverse reactions were minimal. Additional phase II studies are in progress to evaluate the safety and efficacy of lidamidine hydrochloride in the treatment of patients with uncontrolled ileostomy output and in the treatment of patients with chronic diarrhea.

Two open-label studies employing lidamidine hydrochloride as adjunctive therapy in chronic diarrheal disorders have been published (22, 23). In one of these studies, nine patients with inflammatory bowel disease were treated with lidamidine hydrochloride in addition to their maintenance therapy. All patients had more than three bowel movements a day for at least 3 months prior to entering the study. The dose of lidamidine was titrated during a 2-week period until maximum effect was achieved. There was a 33%

decrease in bowel movements per day; all but one patient responded to lidamidine. Participants had an average of 35% fewer bowel movements after the 4 weeks of therapy.

A second open-label study of 17 patients with chronic diarrhea involved patients with Crohn's disease, ulcerative colitis, functional diarrhea, ulcerative proctitis, radiation colitis, and Whipple's procedure. Overall bowel movements decreased 38%, and all but two patients responded. Side effects reported were dry mouth, abdominal cramping, and headache.

This compound has also been employed in an effort to correct gastroduodenal motor dysfunction characterized clinically by chronic pain, nausea, and intermittent intractable vomiting (24). This motor dysfunction consisted of retrograde or disorganized migrating motor complexes and antral dysfunction. Five patients with gastroduodenal motor dysfunction were compared with five control patients. Motility tracings were obtained with a recording probe before therapy and at the end of 5 weeks of medication. This study indicated that motor dysfunction resolved and each patient became asymptomatic and remained so on continuous therapy.

Lidamidine and clonidine possess alpha-2 adrenoreceptor agonist properties, but in certain respects they have different pharmacologic profiles. Clonidine is an imidazoline derivative, whereas lidamidine is an amidinourea structurely dissimilar to clonidine. Whereas clonidine may cause hypotension in animals and humans at antidiarrheal doses, therapeutic doses of lidamidine do not appear to exert either of these effects.

Lidamidine hydrochloride represents a prototype of a new and important group of compounds with interesting effects on the absorption and motor function of the gastrointestinal tract. Further precise, well-controlled studies are needed to determine the efficacy of these agents, their potential value, and possible side effects.

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Current Therapy of Demyelinating Neuropathies

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Our ability to recognize and treat peripheral nerve disease has improved in recent years (1, 2). This is particularly true of the demyelinating or "inflammatory" neuropathies, believed to have an immunological basis (3). Among the various means of categorizing peripheral neuropathies, it has been useful to distinguish those cases which primarily involve the axon cylinders (axonal) from those where demyelination is the predominant pathological feature. In practice, many conditions produce a combination of these two features, and demyelination may be secondary to axonal degeneration. However, this review will deal with several entities in which demyelination is believed to be the primary and initial process, and in which treatments have been actively evolving.

The determination that a neuropathy is demyelinating is made from significant slowing of nerve conductions (often by more than 30%–40%), as tested in the electromyography laboratory (4), and loss of heavily myelinated fibers and segmental demyelination on nerve biopsy, often with varying degrees of onion-bulb formation (5). In conditions such as Guillain-Barré syndrome, the demyelination may only be found proximally and can be demonstrated physiologically with F wave studies, showing slow proximal conduction. The distinction of identifying those neuropathies which are demyelinating is a useful one, as it allows the clinician to approach this subcategory of peripheral neuropathies as potentially treatable conditions.

Guillain-Barré Syndrome

The Guillain-Barré syndrome, also known as acute inflammatory demyelinating polyradiculoneuropathy, was described by Landry in 1859 and Guillain, Barré, and Strohl in 1916 (6). The condition is seen at all ages, and has an incidence of 1–2/100,000 in the population per year (6, 7). Clinically, the syndrome consists of the subacute onset of progressive weakness of more than one limb, which is usually symmetrical and generally begins in the legs and ascends. This is preceded by an upper respiratory or gastrointestinal illness during the preceding month in 60% of cases. Areflexia is generally noted, although present but diminished reflexes may sometimes be found at the biceps and knees. The time course is an important aspect of the diagnosis, as the condition evolves to a peak deficit by two weeks in 50% of patients, by three weeks in 80%, and by four weeks in over 90%. The degree of maximal weakness varies greatly, from mild symptoms not preventing ambulation to severe quadriplegia and respiratory paralysis. Recovery generally begins two to four weeks after attainment of maximal deficit. It may be delayed for months in some patients, while eventual good recovery is seen in approximately 80% of patients.

Other useful diagnostic features include the presence of mild sensory symptoms or signs, autonomic dysfunction (with arrhythmias, postural hypotension, hypertension), cranial nerve involvement in 50% (most commonly facial paralysis), cerebrospinal fluid analysis revealing elevated protein after first week (seen at some point in illness in 80% of cases), and fewer than 10 mononuclear cells (occasional patients show 20–30 cells/cubic mm) (8). Slowing of nerve conduction velocities is seen in 80% of patients at some time during the illness, but does not provide prognostic information (8, 9). F wave studies may demonstrate proximal slowing not evident on rou-

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tine conductions (10). There is evidence that the presence of acute denervation on electromyography (related to axonal degeneration) as well as early reduction in the compound muscle potential amplitude recorded during nerve conduction testing signifies a slower recovery and less favorable prognosis (9, 11, 12). Nerve biopsy is not generally indicated clinically in this condition, where distal involvement of sensory nerves is often not found pathologically (5).

An immunological basis for Guillain-Barré syndrome is suggested by a number of findings, including similarities to experimental allergic neuritis, postinfectious and postvaccination cases, elevation of serum immunoglobulins, circulating immune complexes and antimyelin antibodies, demyelination in rat sciatic nerve produced by Guillain-Barré serum, and reports of rapid and dramatic response to plasmapheresis in patients (3, 5, 13, 14).

The most important tenets of treatment in Guillain-Barré syndrome concern the provision of adequate supportive care. When seen within the first few weeks, patients should be hospitalized in view of the likelihood of progression of symptoms, and should be carefully observed, preferably in an intensive care unit. Particular attention must be paid to respiratory status, with intubation and artificial ventilation performed early when respiratory parameters are affected. Moore et al (15) recommended one or more of the following criteria as indications for artificial ventilation in these patients: (a) clinically obvious cyanotic respiratory failure or distress; (b) arterial hypoxemia P_aO_2 less than 50 torr) and/or hypercarbia (P_aCO_2 greater than 50 torr) on room air; (c) forced vital capacity of less than 1.5 ml/kg body weight; (d) deteriorating respiratory status indicating one or more of the above would soon occur. Artificial ventilation is necessary in 10%–28% of patients (15–17).

Steroids. The efficacy of steroids in Guillain-Barré syndrome is controversial. Some uncontrolled studies report benefit; other reports show unfavorable results (6). A controlled trial of ACTH (100 units intramuscular for 10 days in adults, 2 units/kg daily for 10 days in children) involving 7 patients versus placebo in 8 patients led to a conclusion of a benefit of steroids in Guillain-Barré syndrome. Mean duration to recovery was 4.1 months in the treated group compared to 7.7 months in the nontreated patients. However, severely ill patients requiring respiratory support were excluded from this double-blind study (18). A larger controlled study in Britain of 21 treated patients (prednisolone 60 mg daily for one week; 40 mg daily for 4 days, then 30 mg daily for 3 days) and 19 patients not receiving steroids led to the opposite conclusion (19). Treated patients actually had a less favorable outcome, and this result has prompted reappraisal of the possible benefit of steroids in this condition (5, 6, 17). Anecdotal reports of a good response to high-dose intravenous steroids (20) (125mg methyl prednisolone sodium succinate intravenous every six hours for 48 hours, followed by 30mg Prednisone orally every six hours, tapered over 14 weeks) suggest that some patients may respond well to alternate routes and doses of administration (21). At present, the question of steroid efficacy in Guillain-Barré syndrome remains generally unresolved.

Immunosuppressants. Immunosuppressants have occasionally been used (primarily azathioprine or cyclophosphamide) with anectodal reports of success (17, 22, 23). In an uncontrolled study of 14 patients with severe Guillain-Barré syndrome, cyclophosphamide (40mg/kg/day for 23 days intravenously) administration resulted in an improved rate of recovery, but did not effect ultimate outcome (23). Controlled trials are needed to further assess this treatment modality.

Plasmapheresis. Since the first case report by Brettle et al in 1978 (24) of successful treatment of a patient with Guillain-Barré syndrome with plasmapheresis, many noncontrolled studies have led to favorable reports (3, 6, 25–31). Exchanges have been performed on a daily or alternate day basis, usually for periods of one to two weeks. Improvement may begin after the first or second exchange (or after two weeks), but is not seen in a number of patients (up to 50%) (17, 29). Two multicenter controlled trials of plasmapheresis in Guillain-Barré syndrome are in progress and should provide future guidelines for the use of this modality (32, 33). It may promise to be most effective when used early in the course of weakness of those patients with severe or rapid progression (3).

Chronic Inflammatory Demyelinating Polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) is the term used for a condition which resembles Guillain-Barré syndrome in a number of aspects, but generally has a slower, more gradual onset, and often a relapsing, remitting course. It has been likened to the peripheral nervous system equivalent of multiple sclerosis

(34). Other terms, such as chronic relapsing polyneuropathy and chronic progressive neuropathy, have been used to describe the same syndrome. In one series (35), the symptoms (predominantly weakness in addition to sensory loss) followed a slow monophasic course in 15%, a stepwise progressive course in 34%, a relapsing course in 34%, and a slow progressive course in 15%. Weakness generally progresses to maximum deficit in six to twelve months. Most series include patients with the slowly progressive course as well as those with relapses, which appear as "recurrent Guillain-Barré syndromes" (35–38). Although more common in some series in the 4th to 6th decades, the condition occurs in all age ranges.

Preceding upper respiratory infection is seen less commonly than with Guillain-Barré syndrome, and probably no more than in a control population. The signs on examination consist of a symmetrical polyneuropathy, generally with proximal and distal weakness, and sensory loss. There is areflexia. Several distinctions from Guillain-Barré syndrome include the presence of an action and postural tremor in a few patients, less common cranial nerve involvement (10–16%), and less frequent respiratory failure (8%) (3, 34, 36). Autonomic involvement (incontinence, impotence) is occasionally encountered.

In one series of 53 patients followed for an average of 7.5 years (34, 35), 60% were minimally to moderately disabled, ambulatory, and working; 4% recovered; 8% ambulatory and unable to work; and 28% confined to wheelchair or bed. Mortality rate was 11%. Spinal fluid protein was elevated in 90% of patients (to an average of 138mg%) with a usually normal cell count (mild pleocytosis in 11%). Nerve conduction studies reveal marked slowing (below 60% of normal, in range of 10-28 meters/second) in most cases, and often absent sensory potentials. The nerve conductions tend to remain slow and improve only slightly, even in those responding to treatment (36). Sural nerve biopsy may show segmental demyelination in approximately 23%, and axonal degeneration in a similar percentage. Half the cases show perivascular mononuclear cell infiltrates (34). The sural nerve biopsy may appear normal (5). Immunoglobulin and complement deposits have been found in nerve fibers and intraneural blood vessels from patients (39).

Steroids. Since 1958 (40), steroids have been used in CIDP (progressive and relapsing types) with reported success (34, 41). In a noncontrolled group of 38 patients with CIDP treated with varying doses of prednisone for 3–6 months, Dyck et al (35) reported 39% improved, no effect in 47%, and deterioration in 14%. Dalakas and Engel (36) found prednisone treatment to be effective in controlling the disease in the majority of their 25 patients. A treatment schedule was recommended consisting of prednisone 100mg each day for 3–4 weeks, followed by reduction to an alternate-day schedule over 11 weeks (to 100mg every other day), this dose maintained for 1–3 months before reductions to 10–20mg every other day over the next 3–3½ years. These authors advocated maintenance of low-dose prednisone (10–20mg every other day) indefinitely. Improvement may be rapid, within days, but usually develops over 1–4 weeks (occasionally up to 3–5 months delay).

In a three-month controlled study of prednisone treatment in CIDP (42), doses of 120 mg prednisone every other day were tapered by 20 mg/week until a dose of 20 mg every other day was reached. The drug was then gradually reduced to 0 by the 13th week of treatment. Results indicated a small but significant improvement in the neurologic disability of those patients treated with this regimen, compared to no treatment. Both chronic progressive and chronic relapsing forms responded to the treatment. The recommendation was made to restrict prednisone use in this condition to those patients with a least moderately severe disease because of the potential side effects (42).

There remains some controversy as to the most desirable dose and duration of treatment with steroids, although there is general agreement about their efficacy in a majority of patients with CIDP (1, 5, 34).

Immunosuppressives. Although experience with immunosuppressive agents is more limited, these drugs have been advocated in those patients not responsive to steroids (36). Azathioprine may be used (2.5–3mg/kg/day) with the clinical effect apparent in 1–12 weeks (36, 43). Effective treatment with cyclophosphamide has been reported for oral doses of 2mg/kg/day, 50–150mg/day for 2–9 months, or varying intravenous doses for three weeks (23, 36, 37).

Plasmapheresis in Combination Therapy. There are now numerous case reports of improvement of CIDP following plasmapheresis. Usually the effect is rapid, often beginning after the first or second exchange, and continuing for up to several weeks with additional treatments (28, 29, 44–47). However, the benefit is often temporary and it would appear that complementary treatment with steroids or immunosuppressive drugs is necessary for prolonged remission (3). Plasmapheresis does offer the possibility of rapid, if temporary, results when this is necessary before other treatment modalities become effective, or if they have been unsuccessful (36). A double-blind controlled trial of plasmapheresis in CIDP is currently in progress (34, 48).

Hereditary Neuropathy

Steroids. Dyck et al (49) have described seven patients with clinical features of progressive CIDP who also exhibited signs associated with hereditary motor and sensory neuropathy (Charcot-Marie-Tooth disease) and who improved following steroid administration. Weakness and sensory loss developed over six months to several years in these patients, who also exhibited pes cavus and hammer toes (usually associated with the hereditary neuropathies) and had asymptomatic family members with these skeletal deformities and slow nerve conductions. Additional features suggestive of acquired CIDP included proximal as well as distal weakness and elevated cerebrospinal fluid protein. It was suggested that patients with hereditary motor and sensory neuropathy (Charcot-Marie-Tooth disease) who develop rapid worsening of their condition, with proximal as well as distal involvement and elevated CSF protein (usually normal in Charcot-Marie-Tooth disease), should be considered for a trial of steroids. Questions remain regarding the link between these two conditions (34, 49).

Demyelinating Neuropathy and Malignancies

Demyelinating neuropathies resembling either Guillain-Barré syndrome or CIDP may be seen in association with lymphoma and Hodgkin's disease (5, 50). In patients with multiple myeloma, an associated demyelinating neuropathy is described with sensory loss but predominantly weakness over several months, elevated CSF protein, and marked slowing of nerve conductions. The incidence is highest with osteosclerotic myeloma. Improvement in the neuropathy may occur with chemotherapy for the myeloma. Plasmapheresis has also been reported to be of benefit (5, 51).

Paraproteinemic Neuropathies

Paraproteinemias ("benign monoclonal gammopathy") have been found to be associated with up to 10% of neuropathies without other known cause (52). This has most often been associated with an IgM Kappa gammopathy, which produces a chronic sensorimotor demyelinating neuropathy. Spinal fluid protein is usually elevated, and nerve conductions may show marked slowing. Sural nerve biopsy reveals demyelination as well as axonal degeneration (5, 51). Recent studies have shown that the IgM paraproteins bind to peripheral nerve myelin and are directed against myelin-associated glycoprotein (51–55). There have been reports of improvement in the neuropathy following plasmapheresis, prednisone, and immunosuppressive drugs, although there are no controlled trials (51, 52, 56).

Summary

Demyelinating neuropathies have aroused much interest in recent years as a result of advances in diagnosis, elucidation of underlying mechanisms, and progress in treatment.

A careful analysis of the patient's history, examination, and appropriate laboratory studies (including serum protein electrophoresis and immunoelectrophoresis, CSF analysis, nerve conductions, and electromyography) are essential in evaluating the neuropathies described here.

Diagnostic parameters of the Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy (CIDP) are reviewed. The former should be carefully managed with supportive care, while the efficacy of steroids is controversial, and plasmapheresis may offer an important mode of treatment in some patients. CIDP generally responds well to steroids treatment, but immunosuppressives and plasmapheresis have been used as well. It is likely that some form of immunosuppression will be necessary to complement plasmapheresis in those patients with CIDP responding to this therapy. A group of steroid-responsive patients with hereditary motor and sensory neuropathy with clinical features of acquired CIDP have been described. Paraproteinemia may occur in association with demyelinating neuropathy, which may respond to plasmapheresis combined with immunosuppressive agents.

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Surgical Pathology Notes *Ira S. Schwartz, M.D., editor*

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The pioneering observations of Ilya Metchnikoff, Paul Ehrlich, and Ludwig Aschoff laid the groundwork for our current knowledge concerning the widely dispersed phagocytic cells previously designated the "reticuloendothelial system," now termed the "mononuclear phagocytic system." The case reported on here involves a malignant tumor believed to arise from progenitor elements of this system. The tumor is one of the possible expressions of such neoplasms. Malignant fibrous histiocytoma, to be reported on in future, is a solid tumor (sarcoma), whereas malignant histiocytosis manifests as a widespread lymphoma/leukemia-like disorder. The utilization of ultrastructural and immunocytochemical information is indicative of the common ancestry of these interesting tumors.—ISS

Malignant Histiocytosis

RONLEY PLOUS, M.D.

Malignant histiocytosis is an infrequent, progressive, systemic neoplastic proliferation of histiocytes (1). The entity was first described by Scott and Robb-Smith (2), who called it histiocytic medullary reticulosis. Synonymous and related terms include true histiocytic lymphoma, histiocytic sarcoma, and reticulum-cell leukemia. The disease affects children and adults and typically presents insidiously. The course is usually rapid, with pancytopenia and diffuse organ involvement, especially of the lymphoreticular system. This case report describes the clinical, histologic, immunopathologic, and ultrastructural features as well as the differential diagnosis of malignant histiocytosis.

Case Report. A 28-year-old woman with a one-month history of left axillary lymphadenopathy had a lymph-node biopsy performed at another hospital that was interpreted as angioimmunoblastic lymphadenopathy. Respiratory failure developed, and the patient was admitted to The Mount Sinai Hospital. A transbronchial biopsy showed chronic nonspecific pneumonitis, without evidence of tumor or opportunistic organisms. Biopsies of the left axillary node and bone marrow showed infiltration by malignant histiocytes. The patient received three courses of CHOP (cyclophosphamide, Adriamycin, Oncovin, prednisone) chemotherapy, with resolution of pulmonary symptoms.

Pathologic Findings. The lymph node biopsy consisted of a 4.5 × 3 × 1.8 cm bosselated, pink-tan, soft, rubbery lymph node. Microscopically the nodal architecture was irregularly effaced by sheets of plump oval to polymorphic pale eosinophilic cells with compact nuclei. The nuclei varied in size and shape; many cells showed multiple nucleoli. Mitotic figures were common. The cells demonstrated erythrophagocytosis and emperipoiesis. The malignant process caused an enlargement of the nodal medulla, which spread from the hilar sinuses to the parafollicular sinuses. Isolated follicles with germinal centers were identifiable and were circumscribed by parafollicular sinuses infiltrated by the malignant cells. The medullary sinuses were dilated and solidly filled with the same elements.

The hypercellular bone marrow showed normal hematopoietic cells with paratrabecular replacement by the neoplastic process. Special studies demonstrated positivity for nonspecific esterases (alpha naphthol acetate and butyrate esterases), which was inhibited by fluoride pretreatment, indicating cells of monocytic origin. Immunopathologic studies showed positive staining with MOS1, Ia, OKT11, Leu 3, and B1 antigens. Stains for immunoglobulins, S-100 protein, and alpha-1 antitrypsin were negative.

Ultrastructural studies demonstrated the malignant monocytes to have microvilli, lysosomes, and phagosomes containing lymphocytes. Cyto-

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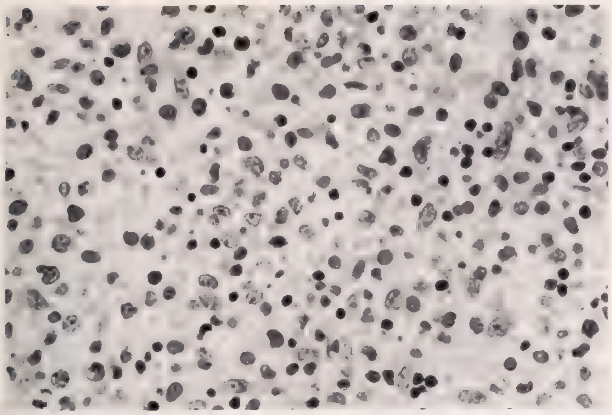

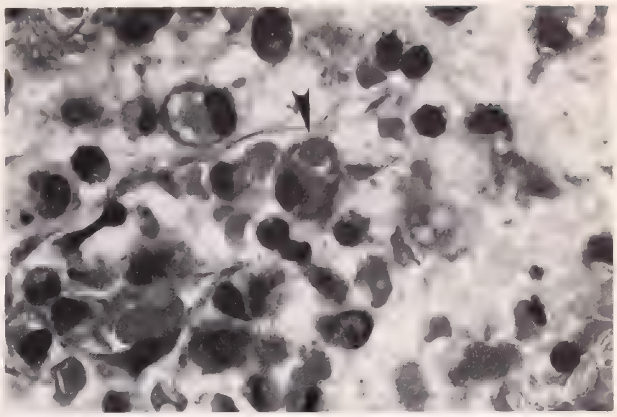

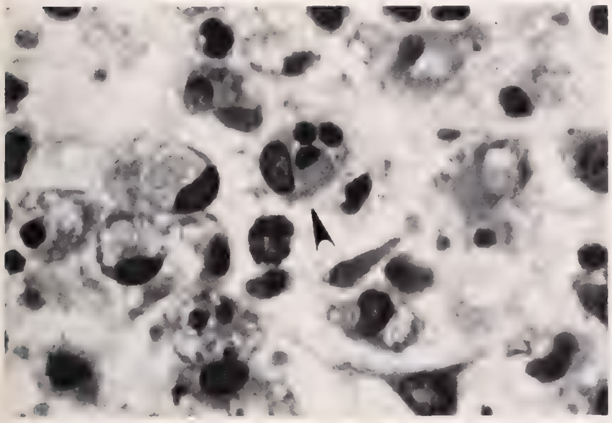

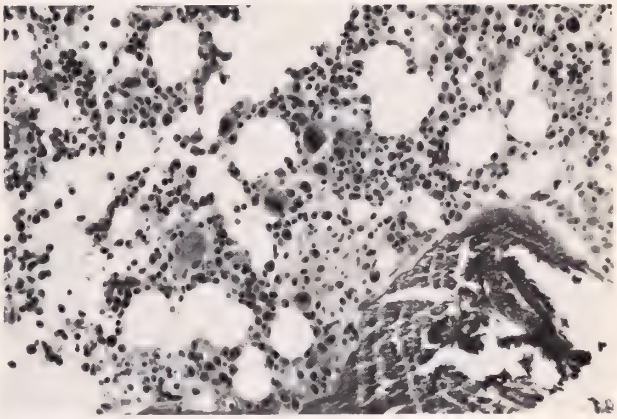

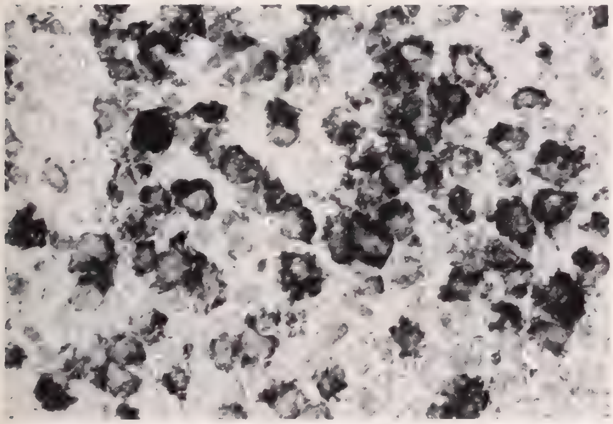

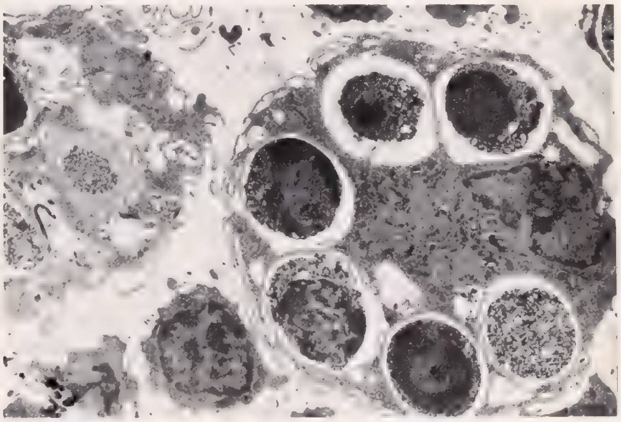

Fig. 1. Top left Sinusoidal infiltrate in lymph node showing pleomorphic malignant histiocytes (H & E, ×350).

Fig. 2. Top right Malignant histiocytes showing erythrophagocytosis (arrow) and cytoplasmic vacuolization (H & E, ×1400).

Fig. 3. Center left Malignant histiocytes, one showing intracytoplasmic leukocytes (emperipolesis) at arrow. A mitotic figure is present (H & E, ×1400).

Fig. 4. Center right Bone marrow biopsy showing a paratrabecular infiltrate of neoplastic cells (H & E, ×350).

Fig. 5. Bottom left Lymph node stained for MOS-1 antigen by PAP method, showing intense reaction (dark cytoplasmic granulation) in many malignant histiocytes (×700).

Fig. 6. Bottom right Electronmicrograph of malignant histiocyte with surface microvilli and multiple phagosomes containing lymphocytes, lysosomes, and an irregular nucleus (×6440).

plasmic rough endoplasmic reticulin, mitochondria, and occasional Golgi bodies were present. The nuclei showed multiple nucleoli and peripheral nuclear heterochromatin.

Discussion. Malignant histiocytosis was first described in 1939 by Scott and Robb-Smith and was designated "histiocytic medullary reticulosis." The disease may occur at any age, although middle-aged and older patients are most commonly affected. The male-to-female ratio is approximately equal (3). The most common symptoms are fever, localized lymphadenopathy, and pancytopenia (4). Careful examination will usually reveal hepatosplenomegaly. Other systemic symptoms, such as respiratory or gastrointestinal complaints, are not uncommon (5–7).

The diagnosis is made by lymph node and/or bone marrow biopsies, which show diffuse infiltration by malignant histiocytes. These cells are characterized by cellular atypia with frequent mitoses, erythrophagocytosis, and emperipolesis. The process spares the nodal capsule and causes displacement and compression of the follicles as the infiltrating cells expand the nodal medulla (hence the name initially given by Robb-Smith).

Cytochemical studies for the nonspecific esterases help identify the cells as monocytic in origin (8, 9), and monocyte-specific antigen can be demonstrated by immunocytologic methods. Cross-reactivity with some B-cell and T-cell antigens may occur (Ia, OKT11, Leu 3, and B1). Immunoglobulins are not present, and if they are demonstrated, an alternate diagnosis such as large-cell (follicular center cell) lymphoma should be entertained (10). Ultrastructural findings characteristically show surface microvilli, phagosomes, lysosomes, mitochondria, rough endoplasmic reticulum, and clumped nuclear heterochromatin (9).

The differential diagnosis of malignant histiocytosis is limited but may prove difficult (4). Large-cell malignant ("histiocytic") lymphoma usually comprises cells with a single nucleolus, absence of phagocytosis, positive immunoglobulin staining and negative esterase enzyme staining. The diagnosis of lymphocyte-depleted Hodgkin's disease is made by finding characteristic Reed-Sternberg cells. The exclusion of Hodgkin's disease may be difficult. Metastatic tumors, especially malignant melanoma, may be differentiated by a tendency of cells to aggregate in nests circumscribed by reticulin fibers, in contrast to individual cellular circumscription in malignant histiocytosis. In addition, cellular junctions are present in ultrastructural studies of carcinomas. Two other entities to consider include Letterer-Siwe disease and sinus histiocytosis with massive lymphadenopathy (Dorfman-Rosai Syndrome), which characteristically involve a much younger population and show uniform benign-appearing histiocytes and a mixed cellular population.

Malignant histiocytosis is a rapidly fulminant disease. Dissemination is characteristic, often involving the spleen, liver, and other visceral organs. Chemotherapy is the treatment of choice (11). The median survival is six months after the diagnosis is made.

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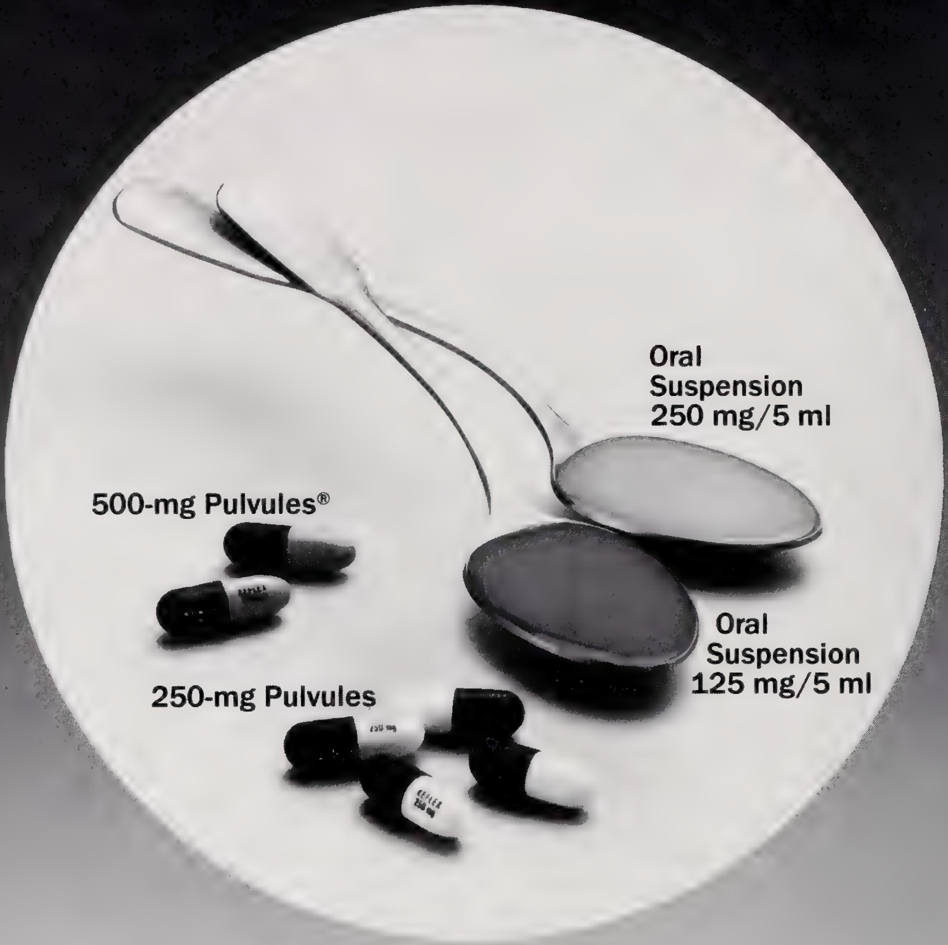
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CONTENTS

CARDIAC ANESTHESIA: THREE DECADES

Introduction *George Silvay, M.D., Ph.D.* 499

Experimental and Clinical Studies with Servo-Controlled Glucose and insulin Administration during Cardiopulmonary Bypass *Pierre M. Galletti, M.D., Ph.D., F. R. Kuntschen, M.D., and C. Hahn, M.D.* 500

Endocrine Response to Cardiopulmonary Bypass *Daniel M. Philbin, M.D.* 508

Adrenergic Response to Cardiopulmonary Bypass *J. G. Reves, M.D.* 511

Three Decades of Cardiac Anesthesia *James F. Arens, M.D.* 516

Intraoperative Diagnosis of Myocardial Ischemia *Steven Konstadt, M.D., Martin Goldman, M.D., Daniel Thys, M.D., Bruce P. Mindich, M.D, and Joel A. Kaplan, M.D.* 521

Monitoring the Left Ventricle: Volume versus Pressure *Daniel M. Thys, M.D.* 526

Right Ventricular Function in the Perioperative Period *Roberta Hines, M.D., and Paul G. Barash, M.D.* 529

Tetralogy of Fallot: Historical Lessons *Valentin Fuster, M.D., and Randall B. Griepp, M.D.* 534

Deep Hypothermic Circulatory Arrest: Current Status and Future Directions *Paul R. Hickey, M.D.* 541

Mechanical Support of the Failing Heart *George Silvay, M.D., Ph.D., and R. M. Koffsky, M.S.* 548

Beta-Adrenergic Blocking Agents: Review and Update *Anthony Squire, M.D., and Joel Kupersmith, M.D.* 553

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CONTENTS *continued*

The Role of Some Noncardiac Factors in Determining Hemodynamic Alterations during Cardiac Surgery *F. G. Estafanous, M.D.* 559

GENERAL ARTICLES

Multiple Synchronous Scar-Related Lung Carcinoma: Case Report and Review *Stewart H. Gleischman, M.D.* 565

SPECIALTY NOTES

SURGICAL PATHOLOGY *Ira S. Schwartz, M.D., editor*

Malignant Fibrous Histiocytoma of the Maxillary Sinus *Pamela D. Unger, M.D., Mamoru Kaneko, M.D., and Swan H. Thung, M.D.* 569

STUDENTS' CORNER

The Etiology of Primary Spontaneous Pneumothorax *Eugene Dula, M.D., and Richard Konsens, M.D.* 575

Correction .... cover 3

Index to Advertisers

Eli Lilly and Company	cover 2
The Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine	cover 3

Bernard H. Eliasberg, M.D.

The Mount Sinai Journal of Medicine
Vol. 52, No. 7, September 1985
Printed in U.S.A.

Cardiac Anesthesia: Three Decades

Twenty-Second Bernard H. Eliasberg Memorial Symposium

Sponsored by the Department of Anesthesiology and The Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine (CUNY) in New York

Held December 3, 1983, at The Mount Sinai Medical Center, New York

Introduction

Dr. Eliasberg graduated from Cornell University Medical College in 1906, and thereupon joined the staff of The Mount Sinai Hospital in New York. He was appointed anesthetist to the hospital in 1910. From 1943 until 1950 he was chief anesthesiologist, and thereafter he was chief consultant in anesthesiology. When he received Mount Sinai's Jacobi Award in 1958, a hospital spokesman described him as "a great teacher who trained hundreds of young physicians in anesthesiology." He died on September 12, 1962 at the age of seventy-six, after more than a half century of association with The Mount Sinai Hospital.

Dr. Eliasberg was a founder of the New York State Society of Anesthesiologists and one of the original members of the American Board of Anesthesiology. In collaboration with Dr. Charles Elsberg, he made major contributions to the development of anesthesia for thoracic surgery.

Through the generosity of the Eliasberg family and contributions from the medical-care industry, we have been able to perpetuate his memory. Initially, this took the form of an evening lecture. Twenty years ago Prof. William W. Mushin of the Department of Anaesthetics, Welsh National School of Medicine, delivered the first Bernard H. Eliasberg lecture, entitled "Quantitation in Anesthesia." Later the format was expanded into a whole day symposium on contemporary problems in the field of anesthesiology. This, we believe, is an appropriate manner in which the lasting contribution of Dr. Eliasberg to our specialty can be honored.

The articles in this twenty-second Eliasberg symposium review the three decades of progress and innovation in cardiac anesthesia and offer leads to the new lines of development needed for further innovations. During these decades cardiac anesthesiology became a subspecialty of anesthesiology, and the two organizations in the United States that provide education in the subspecialty, The Society of Cardiovascular Anesthesiologists and the Association of Cardiac Anesthesiologists, were formed. As James Arens points out in his historical review (presented as the twenty-second Bernard H. Eliasberg lecture during the symposium, on the occasion of receiving the 1984 Eliasberg medal), cardiac anesthesia teams have contributed significantly to the development of optimal monitoring during the surgical procedure and postoperative care.

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Experimental and Clinical Studies with Servo-Controlled Glucose and Insulin Administration during Cardiopulmonary Bypass

PIERRE M. GALLETTI, M.D., PH.D., F. R. KUNTSCHEN, M.D., AND C. HAHN, M.D.

During elective coronary revascularization procedures, diabetics treated in the conventional manner show a higher incidence of cardiovascular complications than nondiabetics (1) (Table 1). They also exhibit widely fluctuating hyperglycemia during and after the operation (2, 3). The glucose received in the priming fluid is not adequately metabolized. Combined with the lipolytic effect of heparinization, this leads to increased free fatty acid utilization which cannot be counteracted without substantial insulin administration. Indeed, the risk of serious metabolic disturbances associated with hyperglycemia in the preoperative and postoperative periods of cardiac surgery (4, 5) is higher in diabetics than in nondiabetics.

Abnormal values of blood glucose in diabetic coronary patients are related to the degree of metabolic control prior to surgery, to the inclusion or exclusion of glucose as an ingredient for the priming fluid of the extracorporeal circuit, and to disturbances of glucose handling in an artificially perfused organism. The stress of surgery and the resulting increase in circulating catecholamines (6, 7) lead to insulin resistance in all patients undergoing cardiopulmonary bypass (8). Several other factors are involved: Sudden mixing of the patient's blood with the priming fluid of a pump-oxygenator circuit containing 5% or 10% glucose is the physiologic equivalent of an intraarterial glucose tolerance test. Cardiopulmonary bypass, particularly when carried out under hypothermic conditions, reduces the perfusion of the muscle mass, an important site of carbohydrate metabolism. Furthermore, the continuous (as opposed to pulsatile) flow characteristics of most blood pumps decrease the action of insulin, as evidenced in experimental perfusions using the "glucose clamp" technique (9).

There has been considerable interest in the concept of myocardial protection by large doses of glucose and insulin in the postoperative period (10, 11). However, such a treatment cannot be effectively implemented in diabetics without close control of the glycemia, since these patients show a considerable degree of insulin resistance immediately after surgery, and several days are needed to return to the status quo ante, even with an uneventful postoperative course (2).

The interactions between metabolic control of diabetes and some corollaries of cardiopulmonary bypass (anesthesia, surgical stress, body temperature fluctuations, cardioplegia, acid-base and electrolyte disturbances, complex pharmacologic support in the intensive care unit, parenteral nutrition, low cardiac output states, depressed renal function) are so complex that optimal support can hardly be achieved with occasional measurements of blood glucose and subcutaneous administration of insulin. Modern techniques for continuous blood glucose monitoring and servo-controlled intravascular administration of insulin allow us to closely follow the biochemical status of patients undergoing cardiopulmonary bypass

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TABLE 1

Frequency of Cardiovascular Complications Associated with Elective Coronary Surgery in Diabetics and Nondiabetics in the Absence of Tight Blood Glucose Control

	Nondiabetics ($n = 467$)	Diabetics (n 60)
In operating room		
Low cardiac output	10.7%	13.5%
Arrhythmias	3.5%	6.8%
In intensive care unit		
Low cardiac output	10.3%	10.0%
Hypertensive episodes	9.6%	15.4%
Ventricular arrhythmias	19.6%	15.4%
Supraventricular arrhythmias	13.1%	37.3%

and to avoid wide excursions of blood glucose levels, as well as overdosage of insulin.

Methods

The standard equipment for feedback-controlled insulin administration is the "artificial beta cell" (12), also referred to in the literature as the "extracorporeal artificial pancreas." It consists (Fig. 1) of a system for continuous blood sampling, a blood glucose sensor, and a minicomputer which, through preestablished algorithms, drives an insulin infusion pump and a glucose infusion pump according to the needs of the patient. Accessories provide a minute-by-minute recording of blood glucose levels, insulin delivery, and glucose delivery.

The blood glucose sensor is a polarographic electrode covered with a gas-permeable membrane to which glucose oxidase has been attached. It requires periodic recalibration if it is to be used for more than a few hours. In practice, blood is sucked continuously at the rate of 2 ml/hr through a double-lumen catheter, which allows the infusion of a minute dose of heparin at the site of blood sampling, thereby preventing thrombosis in the blood glucose analyzer circuit without interfering with the control of coagulation in the pump-oxygenator circuit. Three modifications of the commercial system (Biostator, Miles Laboratories, Elkhart, Indiana) have been found useful for use during cardiopulmonary bypass:

1. The blood sampling catheter must be advanced into a central vein to avoid difficulties related to peripheral vein collapse, which often occurs in total-body perfusion. A special double-lumen catheter has been designed for that purpose.
2. The standard algorithm used by the computer to drive the insulin pump must be modified because at the beginning of cardiopulmonary bypass the instantaneous need for insulin with a glucose-containing prime is greater than with any other stimulus anticipated by the manufacturer of the equipment (13).
3. Close control of blood potassium levels and intravenous potassium administration are necessary whenever large doses of insulin are given to cardiac patients.

The artificial beta cell fits quite comfortably in the operating room (Fig. 1). It can also be used to follow the patient in the intensive care unit, since keeping the patient attached to the monitoring equipment is not inconvenient immediately after cardiac surgery. A portable "open-loop" insulin administration pump decreases the need for nursing supervision and allows mobility once the patient leaves the intensive care unit.

Three forms of supervision of blood glucose levels and insulin needs can be achieved with this instrumentation:

Blood glucose monitoring is the technique employed to investigate the time course of blood glucose levels in response to a particular physiologic intervention without any feedback control from the artificial beta cell, that is, without insulin administration to correct the fluctuations of blood glucose levels.

Blood glucose control is the standard (feedback-controlled) mode of application of the artificial beta cell, which entails an arbitrary choice of the level of blood glucose desired and provides a recording of the rate of administration and the cumulative dose of intravenous insulin needed to achieve that goal.

Blood glucose clamp infuses insulin intravenously at a constant rate to obtain a stable, high blood insulin level (14). The desired value of blood glucose level is arbitrarily selected (typically in the normal range), and the feedback-control capability of the artificial beta cell is then used to measure the amount of intravenous glucose needed to "clamp" blood glucose at the desired level. With this technique, a decrease in the rate of glucose administration signals a decrease in insulin biologic activity.

Results and Discussion

Determinants of Blood Glucose and Insulin Levels in Nondiabetic Patients. All nondiabetic patients monitored during cardiopulmonary bypass exhibit an elevation of blood glucose levels in the absence of any glucose administration (Fig. 2). This increase is due to augmented endogenous glucose production triggered by the release of stress hormones (epinephrine, norepinephrine,

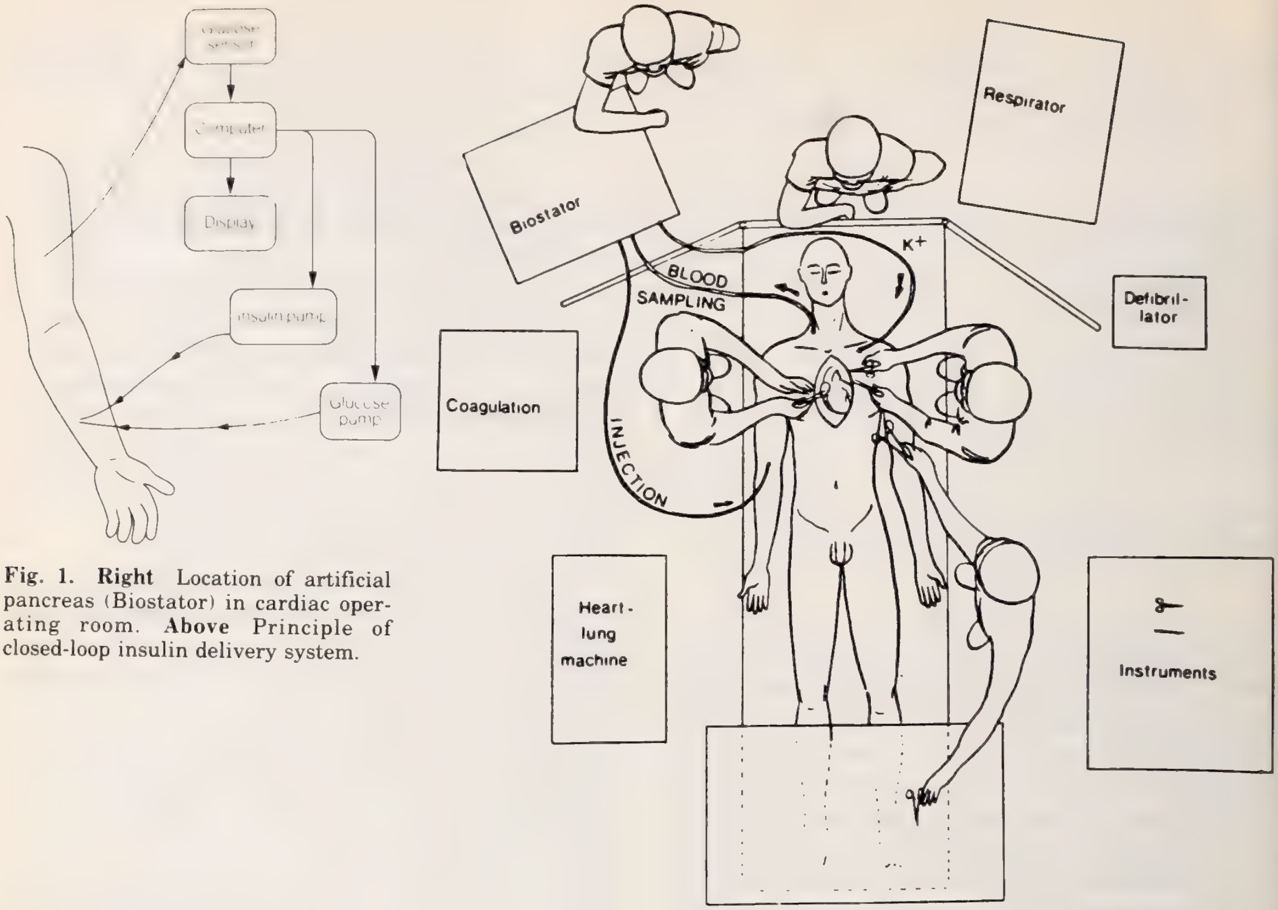

Fig. 1. Right Location of artificial pancreas (Biostator) in cardiac operating room. **Above** Principle of closed-loop insulin delivery system.

cortisol, glucagon, and human somatotropic hormone), which consistently occurs during cardiac surgery (6, 7, 15, 16). However, the time course of blood glucose elevation is different during normothermic and hypothermic cardiopulmonary bypass (Table 2). During normothermia, there is a rapid blood glucose rise at the beginning of cardiopulmonary bypass, and a plateau is reached after about 50 min. During hypothermia, glucose production is inhibited at low temperature, and therefore the rise in blood glucose occurs during the rewarming period. The maximal blood glucose values reached at the end of the operation are about the same with both techniques.

In the absence of insulin administration, when the glucose incorporated in the priming fluid suddenly floods the circulation at the beginning of cardiopulmonary bypass, the peak blood glucose level is the same under normothermia and hypothermia (Table 3). Thereafter, the initial metabolic correction appears to be slower at normal body temperature than at lower temperature, but with the onset of rewarming, the rates of correction are inverse, so that similar blood glucose values are obtained at the end of cardiopulmonary bypass. Increased endogenous glucose production is thought to be the factor that slows down the apparent rate of glucose assimilation by the body tissues under normothermic conditions.

The pattern of glucose assimilation during hypothermic cardiopulmonary bypass is close to that of a standard intravenous glucose tolerance test (Fig. 3). Whereas blood glucose in a normal subject will normally return to control values within 1 hr, the rate of compensation during cardiopulmonary bypass is much more sluggish: the glucose assimilation coefficient (Conrad's K)

TABLE 2

Blood Glucose Levels (in mg/dl) and Blood Glucose Changes (in mg/dl/min) during Normothermic and Hypothermic Cardiopulmonary Bypass in Nondiabetics: No Glucose or Insulin Administration

	Normothermia (n = 8)	Hypothermia (n = 11)
Before anesthesia	88 ± 7	88 ± 5
Before cardiopulmonary bypass	117 ± 11	102 ± 7
At 30 min during bypass	150 ± 20	109 ± 12
End of bypass	173 ± 30	185 ± 19
End of operation	169 ± 48	172 ± 21

TABLE 3

Blood Glucose Levels (in mg/dl) and Blood Glucose Changes (in mg/dl/min) during Normothermic and Hypothermic Cardiopulmonary Bypass in Nondiabetics in Presence of Glucose Load (0.5 g/kg); No Insulin Administered

	Normothermia (n = 10)	Hypothermia (n = 11)
Before anesthesia	81 ± 6	92 ± 5
Before cardiopulmonary bypass	120 ± 8	105 ± 3
Peak value 10 min after start of bypass	460 ± 17	455 ± 5
At 50 min during bypass	342 ± 16	277 ± 15
End of bypass	245 ± 36	246 ± 12
End of operation	206 ± 22	218 ± 6

during surgery is 0.47 ± 0.04 versus 2.2 ± 0.07 in nondiabetic subjects under basal conditions.

Endogenous insulin secretion is not capable of normalizing blood glucose levels during cardiopulmonary bypass. In the absence of exogenous dextrose or insulin administration (Fig. 4, upper panel), endogenous insulin levels increase only slightly during normothermic perfusions and do not increase at all during hypothermic perfusions, in spite of the moderately elevated blood glucose levels reported in Table 2. A sudden glucose load through the priming fluid of the cardiopulmonary bypass circuit (Fig. 4, lower panel) shows that the inhibition of insulin secretion is not total, since endogenous insulin levels rise significantly above preoperative values, particularly in the normothermic perfusions. Yet normoglycemia is not achieved (Table 3).

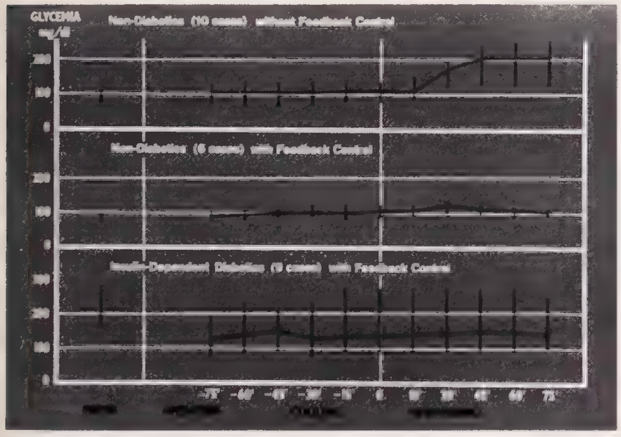

Fig. 2. Average profile of blood glucose levels before, during, and after cardiopulmonary bypass without glucose in priming fluid of extracorporeal circuit in three groups of patients: nondiabetics without servo-controlled insulin administration (simple monitoring), nondiabetics with servo-controlled insulin administration, and insulin-dependent diabetics controlled by artificial beta cell. Vertical segments depict range of individual values. To allow comparison between procedures of different duration, onset of rewarming phase of cardiopulmonary bypass was arbitrarily designated as "zero" time. Reprinted, with permission, from *Trans Am Soc Artif Intern Organs* 1981; 27:241.

The glucose clamp test (Fig. 5) sheds some light on the mechanisms of insulin action during cardiopulmonary bypass in a nondiabetic subject. With a constant rate of insulin administration throughout the operative procedure, an approximately constant plasma insulin level is obtained. The servo-control of the artificial pancreas maintains a constant blood glucose level by infusing appropriate amounts of exogenous glucose. It is apparent that during cardiopulmonary bypass, insulin action is transiently decreased, since the amount of glucose administered is only one-half the quantity required both before and after cardiopulmonary bypass. Thus, not only is endogenous insulin release impaired during cardiopulmonary bypass, but the effectiveness of exogenous insulin is also depressed.

Altogether, glucose and insulin metabolism during cardiopulmonary bypass are affected by a number of phenomena:

1. Insulin secretion is decreased by anesthesia, the release of stress hormones, and unphysiologic blood flow patterns. This inhibition of endogenous insulin secretion is accentuated by hypothermia.
2. Endogenous glucose production is stimulated by the synergistic action of stress hormones

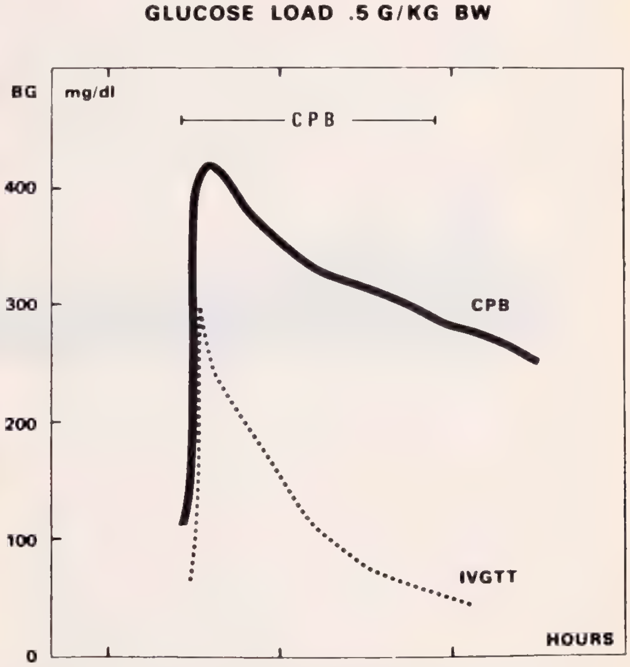

Fig. 3. Normal blood glucose (BG, in mg/dl) response to a sudden glucose load (0.5 g/kg body weight) during intravenous glucose tolerance test (IVGTT) under basal conditions and during hypothermic cardiopulmonary bypass (CPB) with glucose-containing priming fluid.

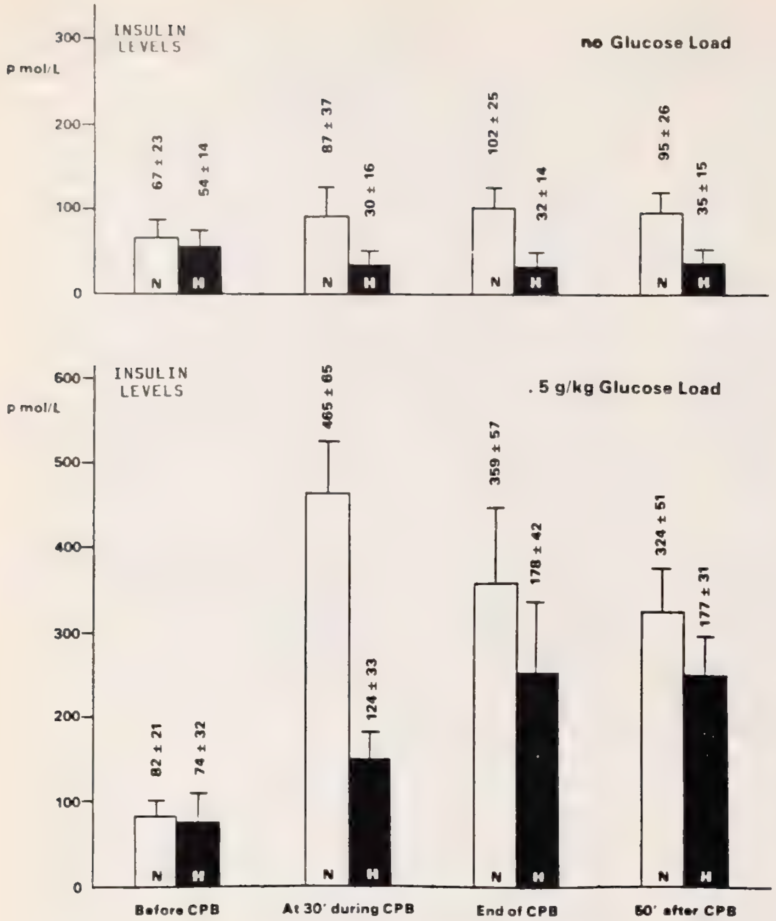

Fig. 4. Insulin levels (in pmol/L) during hypothermic (H) and normothermic (N) cardiopulmonary bypass in nondiabetic patients with (lower panel) and without (upper panel) glucose load of 0.5 g/kg body weight. Mean values ± one SD.

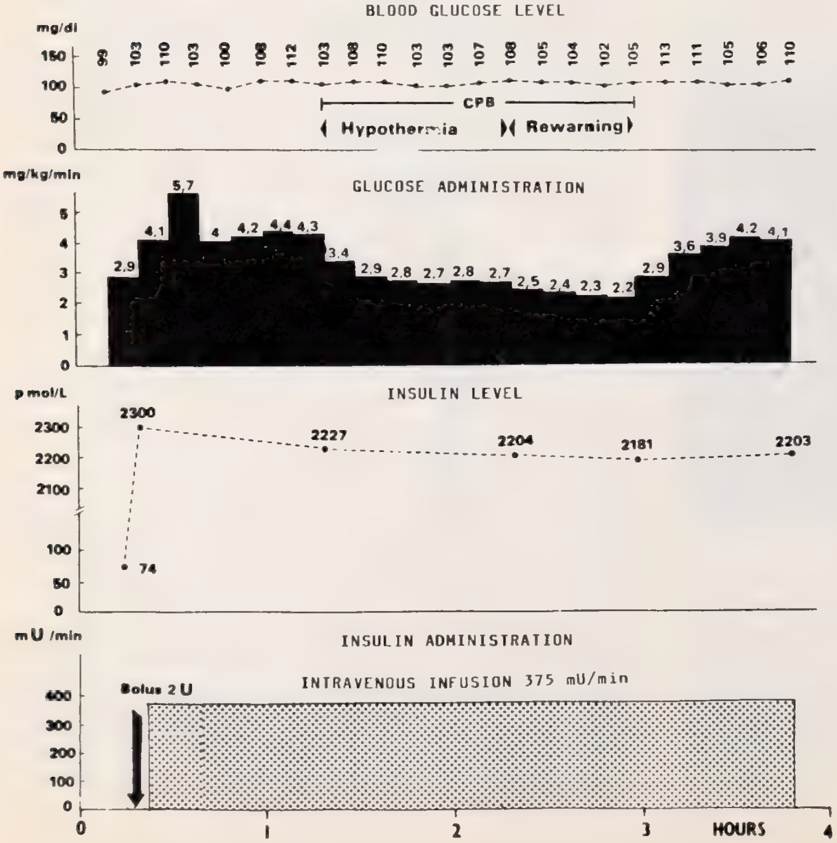

Fig. 5. Glucose clamp experiment in nondiabetic patient undergoing aortocoronary bypass surgery. From top to bottom: blood glucose level (BG) before, during, and after cardiopulmonary bypass (CPB); amount of glucose administered by artificial beta cell at 10-min intervals; levels of insulin in patient's blood; and amount of insulin given to patient (initial bolus 2 U, followed by constant intravenous infusion of 375 mU/min).

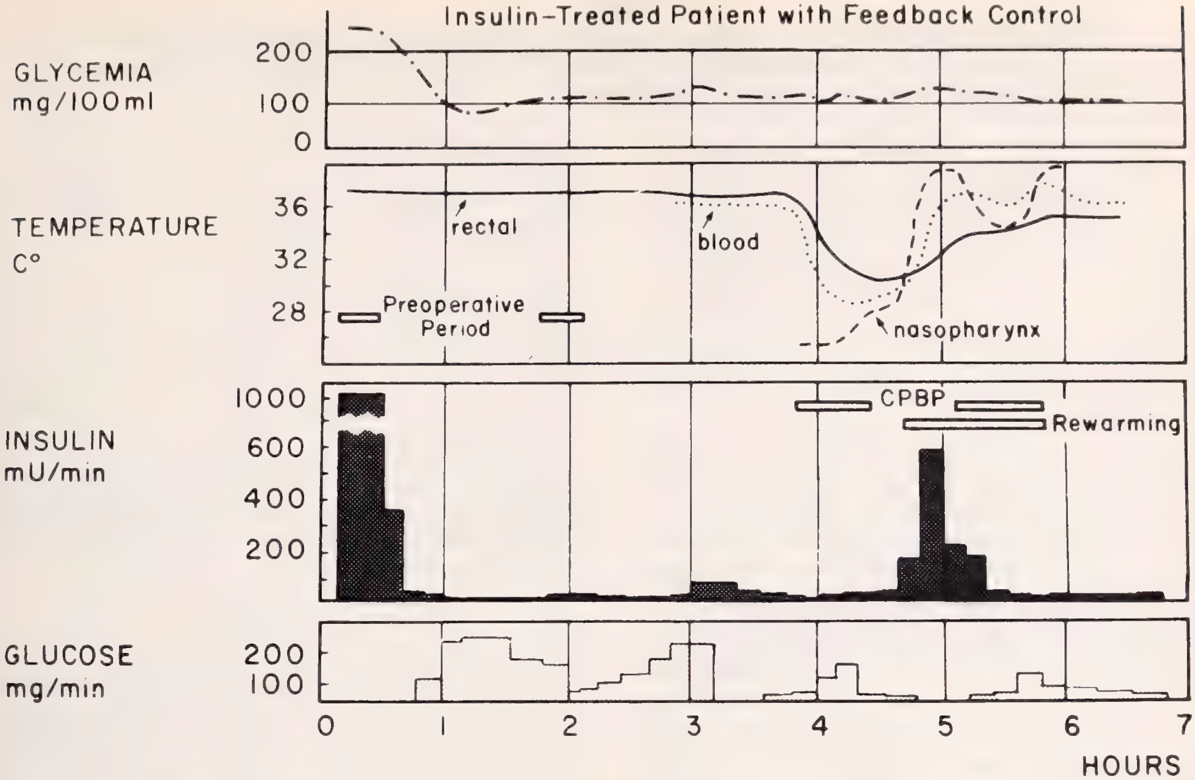

Fig. 6. Time course of blood glucose level (BG, in mg/dl); blood, rectal, and nasopharyngeal temperature (in °C); and amounts of insulin (in mU/min) and glucose (in mg/min) delivered by artificial beta cell to regulate blood glucose level around normal value. Data obtained in insulin-dependent diabetic patient undergoing coronary revascularization procedure under hypothermia in initial phase of cardiopulmonary bypass (CPB). Observe limitations and slight overshoot of servo-control system and interplay between insulin and glucose administration.

without being counteracted by an increase in insulin release. This enhanced glucose production is temperature-dependent and is blocked by hypothermia (17).

3. The endogenous insulin does not exert its full biologic action, as shown by the glucose clamp test. In the period immediately following cardiopulmonary bypass, glucose assimilation at a constant insulin level returns to the preperfusion value, even though stress hormone levels remain elevated, suggesting that the depressed action of insulin during cardiopulmonary bypass depends in part on the abnormal blood flow pattern imposed by the heart-lung machine.

4. The disposal of a sudden glucose load is markedly impaired. Decreased insulin secretion, decreased insulin action, and increased glucose production combine to produce an abnormal rate of glucose clearance during cardiopulmonary bypass.

Blood Glucose Control in Diabetic Patients. Diabetics are prone to serious metabolic disturbances during coronary surgery. To obtain satisfactory control, insulin and glucose must be administered in adequate amounts at the appropriate time. This is illustrated in Fig. 6: The artificial beta cell corrects blood glucose before the start of the operation (with a slight overshoot at the beginning). Throughout the preoperative period, glycemia is maintained at the chosen level by combined administration of insulin and glucose. During the hypothermic phase of cardiopulmonary bypass, insulin needs are minimal. However, rewarming triggers an increase in endogenous glucose production which would otherwise translate to a rapid rise in blood glucose level, but can now be overcome by a rapid and massive insulin administration. With the help of the artificial beta cell, a euglycemic state can be maintained throughout cardiopulmonary bypass.

From a metabolic point of view, cardiopulmonary bypass in diabetics is characterized by insulin deficiency with increased lipolysis, proteolysis, and decreased glucose utilization. This pattern can be favorably influenced by the administration of exogenous insulin in order to provide a more physiologic intermediate metabolism. Studies reported elsewhere have shown an insulin-dose-dependent correction of free fatty acid, glycerol, hydroxybutyrate, and alanine levels during both normothermic and hypothermic cardiopulmonary bypass.

TABLE 4

Comparison of Mean Blood Glucose (MBG), Insulin Requirements, and Glucose Infusion after Hypothermic Cardiopulmonary Bypass in Insulin-Treated Diabetics and Nondiabetics Treated by Artificial Beta Cell and in Nondiabetic Controls Not Insulin Infused

	Diabetics			Nondiabetics			Nondiabetic control group
	MBG (mg/dl)	Insulin (mU/kg/hr)	Glucose (mg/kg/hr)	MBG (mg/dl)	Insulin (mU/kg/hr)	Glucose (mg/kg/hr)	MBG (mg/dl)
Postop day 1							
0–6 hr	130	108	53	131	88	60	183
6–24 hr	117	78	60	138	53	45	175
Postop day 2	122	65	49	121	48	67	140
Postop day 3	152	113	Oral feeding	134	53	Oral feeding	139

Typically, the correction of blood glucose levels during coronary surgery in diabetics requires between 10 and 40 units of insulin. After the operation, the need for insulin is remarkably large, and it decreases rather slowly in diabetics as well as nondiabetics (Table 4). Not surprisingly, insulin-dependent diabetics show a more pronounced insulin resistance than nondiabetics under the same feedback-control program. In the absence of exogenous insulin infusion, nondiabetics are able to normalize their blood glucose by the third postoperative day. In insulin-treated diabetics, the degree of glycemic control achieved by the artificial pancreas immediately after surgery is better than what is observed in nondiabetics without feedback control, in spite of the persistence of derangements of glucose and insulin metabolism associated with the surgical procedure.

During the stay in the intensive care unit, feedback insulin infusion systems are not mandatory to achieve satisfactory blood glucose control in most diabetic patients, since blood glucose fluctuations depend primarily on exogenous dextrose infusion and are therefore predictable. Open-loop insulin delivery systems, such as portable minipumps, can safely provide an adequate blood glucose control as long as exogenous glucose administration is kept at a constant rate and frequent blood samples are obtained to monitor the situation (Table 5).

TABLE 5

Comparison of Glycemic Control (Mean Blood Glucose, MBG), Insulin Requirements, and Glucose Infusion in Diabetics after Coronary Surgery: Open-Loop or Closed-Loop Insulin Delivery

	MBG (mg/dl)	Insulin (mU/kg/hr)	Glucose (mg/kg/hr)
Postop day 1			
Closed-loop	131 ± 20	88	63
Open-loop	129 ± 31	59	52
Postop day 2			
Closed-loop	119 ± 19	66	49
Open-loop	125 ± 23	55	57

Conclusion

Cardiopulmonary bypass to repair cardiac lesions requires a number of physiologic maneuvers that globally impinge on glucose and insulin metabolism. Underlying mechanisms include inhibition of endogenous insulin secretion, depression of peripheral glucose utilization, and reduction of exogenous insulin activity. Although these alterations are not critical in routine cardiac surgery, they may become clinically significant in postoperative states with unusual persistence of stress conditions. They illustrate the complex interplay of hormonal factors which needs to be taken into account to conduct cardiopulmonary bypass under the most physiologic conditions possible.

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Endocrine Response to Cardiopulmonary Bypass

Daniel M. Philbin, M.D.

In recent years interest in investigating the hormonal responses that occur during cardiopulmonary bypass has been notable, no doubt partly because of the availability of accurate and specific assays of hormone levels and partly in the pursuit of "stress-free" anesthesia and surgery, particularly in the management of patients with compromised coronary circulation. The recent attention to hormonal responses also reflects indirectly the remarkable advances in open cardiac surgery in the past few decades. These procedures are now so routine that efforts can be directed to the finer points and the more subtle changes that occur.

Nonpulsatile cardiopulmonary bypass results in a remarkably unphysiologic state. The levels of a variety of hormones substantially increase, presumably in response to the "stress" of bypass.

Antidiuretic Hormone. Early studies concentrating on antidiuretic hormone (ADH) or vasopressin demonstrated that marked increases occurred during the nonpulsatile period; the levels achieved were well beyond the physiologic range for an antidiuretic effect on the kidney and into the range for a potent vasoconstrictor effect (1, 2). Studies in my laboratory utilizing a morphine anesthetic demonstrated ADH levels during the first 30 min of bypass in the range of 24 pg/ml (3). Levels above 10–15 pg/ml are generally considered to be beyond the range for an antidiuretic action on the kidney. The use of hemodilution did not appear to be a significant factor, since similar results were obtained with the use of a blood prime (4).

This is of more than idle interest; in high concentrations, ADH can have a variety of effects on renal blood flow (5) as well as on coronary and splanchnic circulation (6, 7). ADH can also play a role in urinary electrolyte excretion (8) (Table 1).

Catecholamines. The catecholamine response to cardiopulmonary bypass appears to be similar. Although some authors have been unable to demonstrate significant increases in either epinephrine or norepinephrine, most studies suggest that significant increases do occur to levels capable of exerting significant physiologic effects (9–11). Persistence of the elevated levels into the postbypass period may be a real factor in postoperative cardiac function by contributing to increased afterload (12). In addition, the variety of other effects of the catecholamines may contribute to alterations in patient function (Table 2).

Plasma Renin Activity. Plasma renin activity also appears to play a role during bypass, but only in patients who have not been receiving large doses of propranolol, which is known to inhibit renin activity. Studies suggest that in such patients, renin activity increases after institution of bypass, possibly in an effort to maintain or increase systemic vascular resistance (13, 14). However, a number of other investigators have been unable to demonstrate a significant role for plasma renin activity during or after the period of bypass (15–17).

Plasma Cortisol. The response of plasma cortisol levels to the institution of cardiopulmonary bypass is also somewhat controversial. Several investigators have suggested that significant decreases occur, raising the possibility of adrenocortical hypofunction during this period (18–20). Such decreases could not be demonstrated by other investigators (15, 21). In a study utilizing halothane anesthesia, plasma cortisol levels were followed through the period of surgery and cardiopulmonary bypass into the postoperative intensive care unit. What appeared to be a decrease

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TABLE 1
Actions of ADH (Vasopressin)

1. Vasopressor —Direct contraction of smooth muscle
2. Antidiuretic —Increased reabsorption of water
3. Natriuretic —Increased urinary excretion of water
4. Glycogenolysis —Increased glycogen breakdown

TABLE 2
Actions of Catecholamines

	Epinephrine	Norepinephrine
Stroke volume	+ +	+ +
Mean arterial pressure	+	+ +
Peripheral resistance	—	+ +
Renal blood flow	—	—
Oxygen consumption	+ +	0, +
Blood glucose	+ + +	0, +
Blood lactic acid	+ + +	0, +

0, little or no effect; +, + +, + + +, ascending degrees of increase.

in plasma cortisol levels during bypass was in fact not a change in levels when correction was made for the effect of hemodilution (22).

Avoiding Hormonal Increases. Efforts to prevent or attenuate these hormonal increases during bypass have concentrated in two areas: increasing the depth of anesthesia, and modifying the nonpulsatile nature of the flow during bypass.

The use of increasingly larger doses of narcotics, particularly fentanyl, have met with limited success. Significant attenuation of some of the increases in these hormones has been achieved, but total ablation of the response has not been demonstrated (23). Newer and even more potent narcotics such as sufentanil have produced similar findings, at least at the dose levels so far investigated (24).

Modifying the nature of the flow by introducing pulsatile flow during the period of bypass remains at best controversial. A limited success has been reported in attenuating the vasopressin and catecholamine response (17). Others, however, have been unable to demonstrate such an effect (15). A significant reduction in plasma renin activity has also been reported with this modality, followed by a decrease in postoperative hypertension (14). Again, other investigators have found no significant differences (15, 17). It appears likely that most of the differences in results reported by a variety of investigators have as much to do with differences in the technique used to create the pulsatile flow as with the differences in patient population and anesthetic technique (25, 26).

Summary

It is now reasonably well established that marked increases in a variety of hormones, particularly vasopressin, epinephrine, and norepinephrine, occur with the introduction of routine nonpulsatile bypass (Table 3). Attempts to ablate this response have been so far unsuccessful, although considerable attenuation has been achieved. A major question that must be addressed, of course, is whether preventing these responses is beneficial to the patient. It seems reasonable and logical to assume that this massive outpouring of hormones is in response to the unphysiologic state of bypass and that prevention would thus be beneficial. Hard data to substantiate this belief remain to be produced.

TABLE 3
Hormonal Responses to Cardiopulmonary Bypass

Reference	ADH (vasopressin)	Catecholamines		Renin activity	Cortisol
		Epinephrine	Norepinephrine		
Simpson (1)	Increase				
Yamane (2)	Increase				
Philbin (3, 4)	Increase				
Hine (9)		Increase	Increase		
Balasaroswathy (11)		Increase	Increase		
Landymore (14)		Increase	Increase	Increase	
Philbin (17)	Increase	Increase	Increase	No change	
Frater (15)	Increase	Increase	Increase	No change	No change
Taylor (13)				Increase	
Taylor (18)					Decrease
Britt (19)					Decrease
Webster (21)					No change
Philbin (22)					No change

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Adrenergic Response to Cardiopulmonary Bypass

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Abstract

Hypothermic cardiopulmonary bypass initiates a marked adrenergic response in humans. This response is characterized by a prolonged release of epinephrine and to a lesser extent of norepinephrine. The peak rise in these endogenous catecholamines occurs when the heart and lungs are excluded from the circulation and while the patient is being returned to normothermia. The rises in norepinephrine are associated with increases in systemic vascular resistance and perfusion pressure. There is no known harmful effect from these elevated catecholamines, but preliminary data suggest that the particular anesthetic drug and dose can attenuate the adrenergic response to cardiopulmonary bypass.

The abnormal physiologic state of cardiopulmonary bypass produces a marked sympathetic response. In the early experience of cardiopulmonary bypass (1962), 200% increases in norepinephrine (NE) and 1500% increases in epinephrine (E) were reported (1). With the development of more simplified and sensitive assays of catecholamines (2, 3), the adrenergic response to cardiopulmonary bypass has become better characterized. Using these new assays, many investigators have examined the effect of cardiopulmonary bypass on the elaboration of endogenous catecholamines (4–14). It is the purpose of this report to summarize some investigations of the adrenergic response to cardiopulmonary bypass and discuss the implications of the sympathetic response to cardiopulmonary bypass.

Characteristics

The temporal increase in NE and E in relation to the events of cardiopulmonary bypass was studied in 28 patients undergoing various cardiac operations (14). Plasma E and NE were determined by radioenzymatic assays at various stages during the operation. E increased ninefold (from 75 ± 13 to 708 ± 117.3 pg/ml), and arterial NE increased twofold (from 426 ± 66.9 to 825 ± 84.2 pg/ml). In characterizing the temporal relationship of these rises to the events during cardiopulmonary bypass, the peak rises in NE occurred while the heart and lungs were excluded from the circulation (during aortic crossclamp) while the patient was being rewarmed from induced hypothermia. Coincident with the peak rises in catecholamines, the aortic crossclamp was removed so that the postischemic heart was exposed to markedly elevated levels of endogenous catecholamines. Changes in arterial and venous plasma catecholamines parallel each other. The time course and levels of plasma E during cardiac surgery are shown in Fig. 1. A greater rise in E (ninefold) versus NE (twofold) indicates that the predominant adrenergic response to cardiopulmonary bypass is a sympathoadrenal (stresslike) response (14). The E response to cardiopulmonary bypass was similar in magnitude to that reported in patients with syncope (15) and patients with acute myocardial infarction (16). The increased values of NE approached the level reported with strenuous exercise, in orthostasis, and after caffeine (15, 17).

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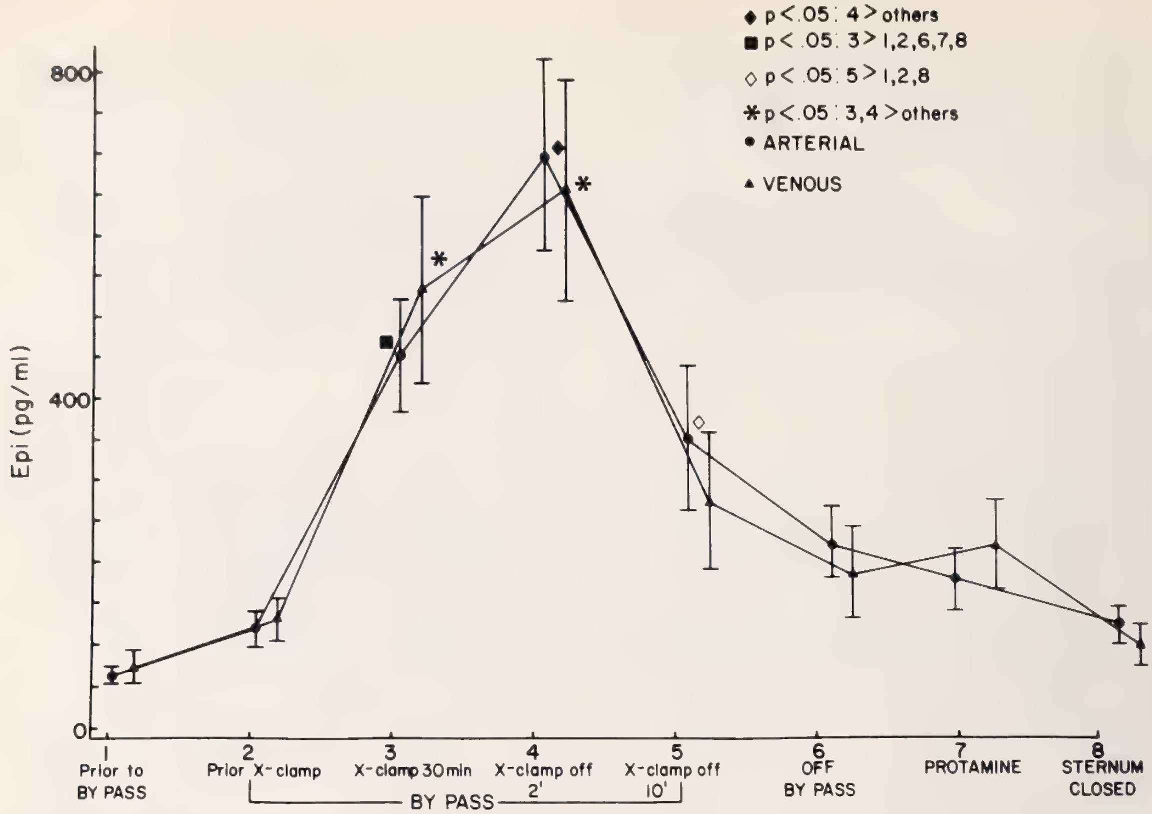

Fig. 1. Mean plasma levels of epinephrine (Epi) during cardiac anesthesia and surgery. Bars indicate SEM. From Reves JG et al. Neuronal and adrenomedullary catecholamine release in response to cardiopulmonary bypass in man. Circulation 1982; 66:49–55, by permission of the American Heart Association, Inc.

Causes

The precise cause and mechanism by which the marked sympathetic response to cardiopulmonary bypass occurs are not known. The elaboration of endogenous catecholamines probably results from a combination of an increase in elaboration and a decrease in clearance (metabolism) of catecholamines during cardiopulmonary bypass.

A partial list of factors known to precipitate the release of catecholamines during cardiopulmonary bypass includes hypothermia, hypotension, hypovolemia, nonpulsatile flow, hemodilution, insulin release, prostaglandin release, myocardial ischemia, hypoperfusion, and renin release. Each of these physiologic conditions is associated with a release of endgenous catecholamines, and the combination of these stimuli during cardiopulmonary bypass constitutes a potent stimulus for the release of E and NE.

Contemporaneous with these factors are conditions which contribute to decreased clearance of plasma catecholamines. Clearance of catecholamines occurs primarily in richly sympathetically enervated organs of the body. Two such organs, the lungs and heart, are excluded from the circulation during the time that catecholamines peak during cardiopulmonary bypass; thus, clearance may be reduced. Liver perfusion is also reduced during cardiopulmonary bypass, and this may account for some reduction in clearance of the catecholamines. Finally, during hypothermia all enzymatic reactions are reduced in direct relationship to the reduction in temperature; therefore, during hypothermic cardiopulmonary bypass the metabolism of catecholamines, which is enzyme dependent, is reduced in all organs.

In attempting to determine the specific causes of release of catecholamines, the effects of the temperature, change in systemic flow, change in the venous pressure, and change in mean blood pressure were all correlated with changes in NE and E to determine a cause-and-effect relationship. This type of univariate analysis failed to show any correlation of these single variables with the changes in catecholamines (14), suggesting that no single variable is responsible for the elaboration of catecholamines during cardiopulmonary bypass, but rather that a complex interaction of many variables must initiate the adrenergic response.

Implications

Although the rise in catecholamines during cardiopulmonary bypass is well documented (4–14), the physiologic and pathologic consequences of these rises are poorly understood. The Table lists potential implications of the rise in catecholamines during cardiopulmonary bypass. The most certain physiologic effect of the release of catecholamines during cardiopulmonary bypass is the positive association between the increases in NE and mean systemic pressure during aortic crossclamping (8, 14). The association of NE with mean arterial pressure is explained by a significant ($p < 0.03$) association of plasma NE levels with systemic vascular resistance ($r = 0.52$). Thus, as plasma norepinephrine increases during the crossclamp interval during cardiopulmonary bypass, there is an increase in systemic vascular resistance and mean perfusion pressure. The elevations in perfusion pressure have implications for myocardial protection, since increases in the perfusion pressure may wash out myocardial protective cardioplegic solutions via increased noncoronary collateral flow to the heart (18). The ensuing cardiac rewarming and washout of myocardial protection fluid (cardioplegia) could impair myocardial protection during the ischemic crossclamp interval.

Another potential adverse consequence of elevations of catecholamines during cardiopulmonary bypass occurs during heart reperfusion. The postarrested heart may be vulnerable to catecholamine damage (19, 20). Reperfusion with catecholamine-rich plasma could adversely affect cardiac replenishment of ATP by increasing oxygen demand at this time (21). The hypothesis that reperfusion of the postarrested heart with elevated endogenous catecholamines might contribute to myocardial damage has recently been

TABLE

Implications for Myocardial Protection of Catecholamine Release during Cardiopulmonary Bypass

During elective myocardial hypoxia (crossclamp)
- Increased systemic vascular resistance (increased systemic pressure = cardioplegia washout)
- Increased myocardial metabolism

During myocardial reperfusion
- Coronary vasoconstriction
- Increased myocardial metabolism
- Arrhythmogenesis

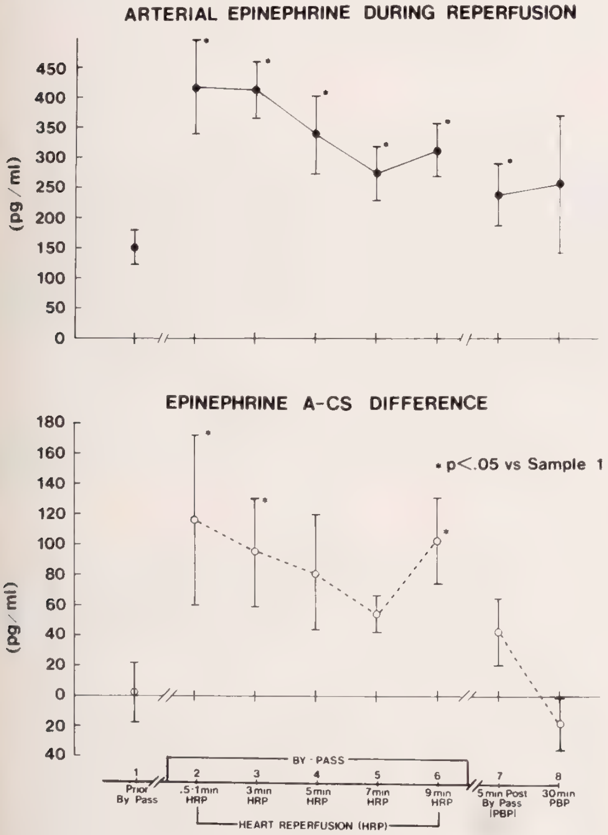

Fig. 2. Arterial epinephrine (E) levels and E arterial-coronary sinus (A-CS) difference before bypass, during heart reperfusion (HRP), and after cardiopulmonary bypass (PBP). Arterial E is increased during HRP and return to prebypass values after bypass. During HRP heart extracts E, as indicated by significant positive A-CS difference. From Reves JG, et al. Elevated catecholamines during cardiac surgery: consequences of reperfusion of the postarrested heart. Am J Cardiol 1984; 53:722–728, with permission.

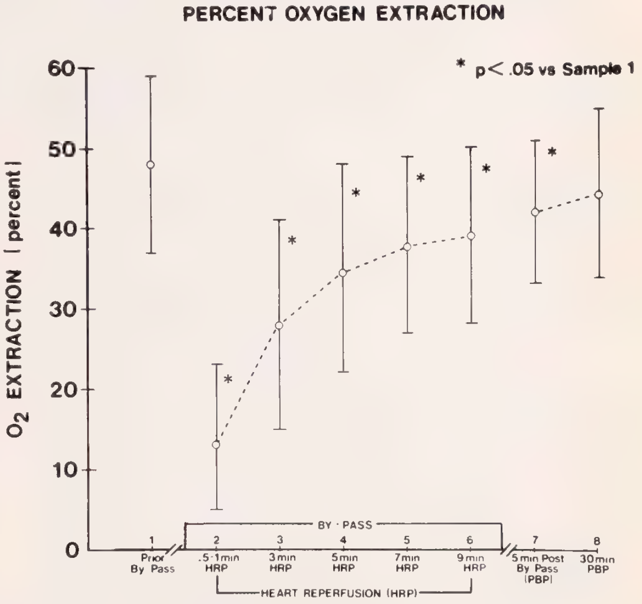

Fig. 3. Percent oxygen extraction before bypass, during heart reperfusion (HRP), and after cardiopulmonary bypass (PBP). Oxygen extraction was computed from oxygen content of arterial and coronary sinus blood. Oxygen extraction is markedly reduced during early reperfusion. From Reves JG, et al. Elevated catecholamines during cardiac surgery: consequences of reperfusion of the postarrested heart. Am J Cardiol 1984; 53:722–728, with permission.

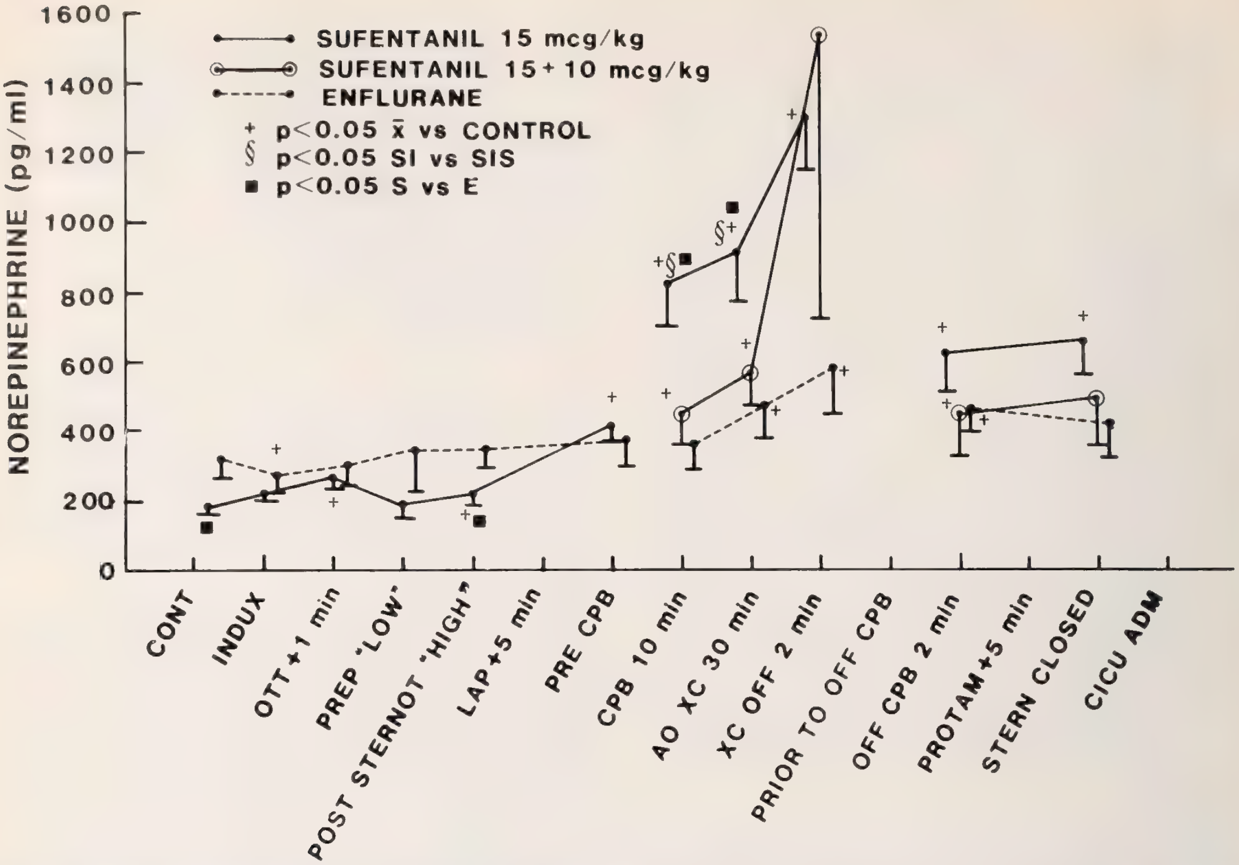

Fig. 4. Plasma norepinephrine (pg/nl) at various time intervals in patients anesthetized with enflurane and two dosages of sufentanil. Note that enflurane given during cardiopulmonary bypass (CPB) is accompanied by a significantly lower norepinephrine response. Patients given sufentanil (15 μg/kg) plus additional sufentanil (10 μg/kg) just prior to CPB tend to have lower norepinephrine values than those not supplemented. CONT, control (baseline); INDUX, induction of anesthesia; OTT + 1 min, orotracheal inbutabion; PREP "LOW", nadir of hemodynamics during preparation and draping of patient; POST STERNOT "HIGH", zenith of hemodynamics during surgery: LAP + 5 min, 5 min after placement of left atrial catheter; PRE CPB, prior to CPB; CPB 10 min, CPB 10 min; AO XC 30 min, 30 min aortic crossclamp; XC OFF 2 min, aortic crossclamp removed 2 min; PRIOR TO OFF CPB, prior to discontinuation of CPB; OFF CPB 2 min, 2 min after discontinuation of CPB; PROTAM + 5 min, 5 min after protamin administration; STERN CLOSED, after sternal closure; CICU ADM, admission to cardiac surgical intensive care unit. Data from Paul N. Samuelson, M.D., unpublished.

examined (13). In 60 patients undergoing coronary artery bypass surgery, NE and E significantly increased. There was significant heart extraction of epinephrine during reperfusion of the heart, signified by the positive aortic-coronary sinus E difference (Fig. 2). Despite the significant uptake of E during reperfusion, there was no association of the values of E or E uptake with indicators of myocardial damage (CK-MB). Likewise, there was no correlation between the rises in NE or gradients of NE across the heart with CK-MB.

Several explanations may account for the failure to demonstrate a relationship between the reperfusion of the heart with catecholamines and myocardial damage, including the following:

- Myocardial protection during the ischemia was sufficient to preserve adequate cardiac energy stores to meet any increased demands imposed by elevated E.
- NE and E during reperfusion were not sufficiently high enough to increase metabolic requirements.
- The causes of myocardial damage during cardiac surgery are many; the contribution of NE and E to injury during reperfusion may be so small that other more prominent factors obscure their effect.
- There is evidence that despite the elevated E and NE during reperfusion, percent oxygen extraction of the heart during immediate reperfusion is actually reduced (Fig. 3). Thus, the uptake of E did not increase oxygen extraction. This may explain the lack of adverse effect of catecholamines on myocardial protection during reperfusion.

It is theoretically possible that the increase in catecholamines might precipitate arrhythmias during cooling of the heart before crossclamp or during reperfusion of the heart in the postischemic period. This relationship has not been studied well.

Modification by Anesthetic Drugs

A wide variety of anesthetic management techniques have been used in patients undergoing cardiac surgery. Several investigations have documented the rise in catecholamines with various anesthetic techniques during cardiopulmonary bypass (4–14). In general in this procedure, all anesthetic techniques are accompanied by a pronounced adrenergic response. Properly designed randomized studies comparing various anesthetic techniques during cardiopulmonary bypass addressing the rise of catecholamines have not been performed. Likewise, dose-response studies establishing a dose-response mechanism in attenuating the catecholamine response to bypass have not been conducted.

It may be inferred from some unpublished data (Samuelson et al) that enflurane attenuates the release of epinephrine more than sufentanil (Fig. 4). Furthermore, from these data a dose-effect relationship with sufentanil is evident; patients given a supplemental dose of sufentanil tended to have a reduced catecholamine response to cardiopulmonary bypass. These data suggest that the specific anesthetic agent as well as the dose of anesthetic agent may be important in attenuating the adrenergic response to cardiopulmonary bypass.

Intuitively it would seem that there would be advantages to the attenuation of the catecholamine response to cardiopulmonary bypass, but no data have convincingly demonstrated that the adrenergic response to cardiopulmonary bypass is harmful.

Summary

There is a potent adrenergic response to cardiopulmonary bypass that is just one of many humoral reactions to the abnormal physiologic state induced by extracorporeal circulation of blood and exclusion of the heart and lungs from the circulation. Although the sympathetic nervous system response to cardiopulmonary bypass is marked, no data have demonstrated that this adrenergic response contributes to an unsuccessful outcome for the patient.

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Three Decades of Cardiac Anesthesia

James F. Arens, M.D.

After only thirty years of development, cardiovascular anesthesiology already has a rich tradition. The first paper devoted to cardiac anesthesia, "Anesthesia in the Surgical Treatment of Congenital Pulmonary Stenosis," was from Johns Hopkins' Merel Harmel and Austin Lamant and was published in *Anesthesiology* in 1946. In 1951, Ken Keown reported on the anesthetic management of closed mitral commissurotomies. William McQuiston, working with Willis Potts at Children's Memorial Hospital in Chicago, introduced surface cooling to deal with severely hypoxic children. From these experiences, Arthur Keats extracted some important early conceptual contributions of anesthesiologic experience in closed-heart surgery:

- Safety of tracheal intubation in children.
- Understanding of the hemodynamic effects of controlled respiration.
- Resolution of the "curare-death" issues by succinylcholine.
- Continued use of some preoperative drugs and discarding of others.
- Hazards of diuresis and fluid restriction.
- Understanding of the effects of anesthetics on the heart and regional circulation.
- Appreciation of benefits of hemodilution and hazards of polycythemia.

Anesthesia in Open-Heart Surgery

A brief history of anesthesia as it was developed for open-heart surgery is presented here, with the intention of looking at our past errors and accomplishments to gain perspective on our current techniques and to bring to the fore the important scientific principles established in the practice of cardiac anesthesia, some extended to other areas of medicine, to augment Arthur Keats' formulation.

John Gibbon proved the feasibility of total cardiopulmonary bypass in experimental animals in 1939, but first successfully repaired an atrioseptal defect in 1953, in a 17-year-old girl. However, the first patient, and four subsequent patients, died.

As best as I can document, it was nurse anesthetists who worked with Gibbon, although Hampton Jennings later went to Jefferson.

In 1951, Clarence Dennis and Karl Karlson used extracorporeal circulation to repair an atrioseptal defect at Minnesota. The patient was anesthetized with cyclopropane by Fred Van Bergen and Joe Buckley. However, the patient failed to survive because of pump problems.

John O'Donnell and Tom McDermott in 1953 at Georgetown worked with Charles Huffnagel to perform aortic valve insertions in the descending aorta for wide-open aortic insufficiency.

In 1954, Lillihei at Minnesota used controlled cross-circulation to perform the world's first successful closure of a ventricular septal defect. Fred Van Bergen and Joe Buckley gave the patient cyclopropane, and the father as donor was given thiopental, curare, and nitrous oxide by Jim Matthews and Earl Schultz.

In 1955, John Kirkland at the Mayo Clinic successfully repaired a ventricular septal defect in a 5½-year-old child using a Mayo Gibbon oxygenator. Bob Patrick was the anesthetist and used N_2O, O_2, and ether.

In 1955, open-heart anesthesia was done at Johns Hopkins by Olive Berger and Edith Rieder, certified registered nurse anesthetists. Don Benson became involved in 1956 and started using ventilatory support for 24–48 hr postoperatively. The report on this experience was published in December 1959.

In January 1956, Denton Cooley repaired a ventricular septal defect at Texas Children's Hospital, and Arthur Keats provided the anesthesia.

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As far as I can document, the first open-heart surgery on an adult was on a man who developed a ventricular septal defect secondary to an infarct that Denton Cooley repaired, in what was roughly his tenth open-heart procedure. Inductions were performed with cyclopropane followed by light ether oxygen.

Scannell operated on a 10-lb, 6-month-old infant for a ventricular septal defect at the Massachusetts General Hospital on November 23, 1960. Phipps Hallowell and Thorhild Anderson administered Pentothal, N_2O, O_2 succinylcholine drip. The child died postoperatively of respiratory distress syndrome.

In 1961 at the Massachusetts General Hospital Phipps Hallowell, Henrich Bendixen, and John Hedley-White were the cardiovascular anesthetists. To quote Ed Lowenstein, who joined that group in 1965, Mike Laver in 1961 was in his "the only worthwhile anesthesia is done on dogs" stage.

In 1966, Jack Viljoen joined the Cleveland Clinic group and attempted to organize cardiovascular anesthesia. All attempts to alter the status quo failed until he befriended Don Effler on the squash court. Among Viljoen's major contributions are the introduction of the use of nitroglycerin and focusing attention on problems with propranolol.

In 1967, Harry Wollman and Alan Ominsky "proclaimed" themselves, as they put it, cardiac anesthetists. "We walked into a room where monitoring consisted of an EKG and an arterial line inserted through a cutdown by the surgeons. . . . We had no oscilloscopes and used a Grass polygraph to record the arterial pressure and EKG. . . . Almost all our cases breathed spontaneously at the end of the case and the sick mitrals had tracheostomies performed on the table, but were often not ventilated" (HW, personal communication).

In July 1966, when I got out of the service and joined the Ochsner Clinic, the heart room was hell—no one wanted to work there. My interest in the pump developed because our one and only pump technician was an unreliably controlled epileptic.

In 1966, the Vineberg was the big operation, and Earl Wynands made many noteworthy observations while working with Arthur Vineberg. Because of the Vineberg operation, we all learned a lot about "bring back" hearts.

Changes in Technique. It was at this point that all anesthesiologists doing coronaries realized that our usual techniques did not work for these cases.

One result was an alteration in choice of anesthetic agent—thus the change to morphine at Massachusetts General, to methoxyflurane at Cleveland, and so on.

Equally important was the recognition of the need to monitor the patient even prior to and during induction. The first Vineberg patient I anesthetized was placed in an induction cubicle 50 yd from the operating room. I gave a 50-mg test dose of Pentothal, and the case was over. An unsuccessful resuscitation followed. This was my third day at work.

Many attributed the sudden improvement in anesthesia techniques, especially in anesthetic agents, to improved anesthesia care. However, in retrospect, much credit has to be given to improvements in monitoring, skills, techniques, and equipment. The placement of the early plastic non-Teflon arterial lines could consume more time than any of us care to admit; however, even this was a big improvement over the Cournand needle. But change comes slowly. A good anesthesiologist came to observe our techniques, especially monitoring. He said it all looked very complicated to him. I asked him what his mortality rate was on coronaries. "We do well," he replied. "Our mortality is only 25%." I told him I thought he could change that. In Keown's book *Anesthesia for Surgery of the Heart,* he says, "Surgery for coronary artery disease using a revascularization technique described by Vineberg will result in a mortality rate of approximately 20%."

Arthur Keats has made the interesting observation that many of the advances in open-heart surgery were made at non-medical-school hospitals. Why? Perhaps because the surgeons in academia could never get ten successive dogs to survive cardiopulmonary bypass and therefore were forbidden by the medical school hierarchy to do open-heart surgery on people.

Teamwork by Specialists Develops. Suddenly teams were born—one of the reasons probably was that no anesthesiologist working alone could balance those eight-channel Hewlett-Packards. Blood gas laboratories were literally carved out of, or into, the operating room suite because a 4-hour turnaround time for a gas was a bit long.

Once surgery for coronary artery disease became a fact of life, sufficient volume developed that more anesthesiologists devoted more and more time to cardiac anesthesia. Nurses specialized in operating-room techniques, monitoring teams developed, the same anesthesiologists worked with the same surgeons many times, for reasons of efficiency as well as effectiveness. Cardiologists found they were no longer needed in the operating room because they learned that anesthesiologists really knew something about arrhythmias and therapeutic pharmacology. Cardiologists, surgeons, and anesthesiologists discussed upcoming cases—and as a result there were indeed fewer surprises. Blood banks became more efficient, and improved screening techniques for typing were developed. Anesthesiologists became involved in postoperative care, partly because surgeons busy in the operating room were unavailable. Corners of recovery rooms were reserved and specifically set up for heart cases, and the same interested nurses always took care of the "hearts." Suddenly recovery rooms were crowded; a new area was built or remodeled and called an intensive care unit, and the ICU became a fact of life. (A few ICUs were organized prior to 1965—but not many.)

Managing Respiratory Problems. Respiratory problems in the early days of heart surgery were common; so was immediate extubation. Out of frustration, I, like the others, began to ventilate cardiac patients prophylactically. Our heart surgeon said this was unnecessary. I pulled charts on all the heart cases in a 5-year period prior to 1966 and found a postoperative tracheostomy rate of 25%. No more arguments were forthcoming. At this point, in a 550-bed major hospital, there were two Bird ventilators stored in central supply. Therefore, a respiratory therapy department had to be developed. Fellow anesthesiologists, nonheart surgeons, and recovery room nurses thought all this was ridiculous, and ventilatory care was made difficult; rules had to be established to allow nurses to give intravenous narcotics routinely. One was forced to use controlled ventilation with sedation or paralysis so that the "tube" could not be pulled by a colleague. Every iatrogenic complication was a political, medical, and nursing crisis. Physicians were very concerned when volume ventilators were first used, because they had no disconnect alarms. Bird ventilators emitted a continuous flow of air from the machine and one could hear the disconnect. We had to be able to trouble-shoot every ventilator ourselves; today, unfortunately, that is a lost art—the price of superspecialization.

Finally, patient survival improved, and suddenly everyone had known all along that ICU care was necessary. Anesthesiologists and surgeons became more knowledgeable, comfortable, and familiar with ventilators. When "Vietnam" lung became a recognized entity, larger numbers of noncardiac patients were ventilated with expertise and confidence.

Contributions that have come from pediatric cardiac anesthesia are more difficult to define than those from anesthesia for adults. Certainly, pump techniques and equipment have been upgraded to meet the challenges of "pumping" neonates. Skills have been improved to meet the challenge of monitoring these infants. However, much of the knowledge about ventilating babies has come from neonatal units and not from pediatric heart patients.

Extracorporeal Circulation and Invasive Monitoring Extended to Noncardiac Patients. As anesthesiologists and surgeons became more comfortable with extracorporeal circulation, it is not surprising that attempts were made to use extracorporeal circulation for patients with deteriorating respiratory distress syndrome. Thus, in the late 60s, the first attempts with extracorporeal membrane oxygenators were made in the United States. One of the first membrane oxygenators in the United States was developed by Ed Lande, who was at the time, I believe, a second-year surgical resident at Cornell. At Ochsner we used these oxygenators on the third pediatric cardiac patient in the United States; unfortunately, the girl died. Much was learned about the need for different types of tubing, for regional heparinization, for different types of cannulation, for large teams to work 24 hours a day for 2–3 days.

Reports of malignant hyperpyrexia being treated by extracorporeal circulation are not surprising; the idea arose out of the close working relationships between surgeons and anesthesiologists.

One of the reasons, I am sure, that the pump is not used more by neuroanesthetists and neurosurgeons is that they are unfamiliar with both the apparatus and the team who uses it. Cardiac anesthetists often know little about neuroanesthesia and therefore also tend to be uninvolved in the problems of such procedures.

We learned to use arterial lines, cardiovascular pumps, Swan-Ganz catheters, EEGs—and suddenly noncardiac patients posing difficult treatment problems were being invasively monitored, as the usefulness of our experience became clear. Many individuals, and many groups, have made contributions—Ted Stanley with fentanyl hemodynamics, the Emory group, the Birmingham group, the Stanford group, the New York University group, and many others have pushed cardiac anesthesia forward.

In sum, to Keats' list of conceptual contributions by early cardiac anesthesiologists, I add these others:

- The anesthesiologist became an integral part of the surgical team.

- The anesthesiologist became an integral member of the intensive care unit; even, in many units, the director.
- Laboratories serving acute-care patients became routine.
- Pulmonary care services fluorished only when cardiac surgery made intensive postoperative respiratory care necessary. In the early 60s, the incidence of tracheotomy ranged between 10% and 20% of all open-heart cases.
- Ventilator usage came to be taken for granted.
- Invasive monitoring was born.
  a) Rochester needles replaced Cournand needles.
  b) Intrajugular vein lines replaced extrajugular vein lines.
  c) The subclavian approach became a part of the anesthesiologist's armamentarium.
  d) The Swan-Ganz catheter brought the use of the Starling curve into everyday use.
- Narcotic anesthesia was reborn.
- Inotropes and vasodilators came out of the closet.
- Membrane oxygenators were to be the solution to slow surgery—an intriguing conceptual product that has never worked out.
- The importance of the expertise and research lodged in various equipment manufacturers was highlighted. Although we are all at times critical of manufacturers, where would we be without the Hewlett Packards, the Edwards Laboratories, the Ayerst Pharmaceuticals, to mention just a few?

What Lies Ahead?

Effects of Subspecialization. Subspecialty development within anesthesia—whether pediatric, obstetric, cardiac, neurologic, vascular, pain, or ICU—is a fact of life. Why does it happen? Most often, a large volume of certain kinds of cases develops and then someone becomes interested or is assigned to take an interest, in that subspecialty. Suddenly, the cases go better, the surgeon develops a better attitude, the anesthesiologist becomes and knows that he is an important team member—yes, even a second primary physician—and knows it; and the operating room team becomes a stable perioperative entity. Ideas are exchanged between a select few anesthesiologists with similar interests. Suddenly someone says, Let's meet, and a society is born, a subspecialty is born. The Association of Cardiac Anesthesiologists was formed on September 30, 1972, with B. Dalton as president, Emerson Moffitt as vice-president, and Ed Lowenstein as secretary. However, the association has a limited membership of fifty. Because of that limit, in 1978 the Society of Cardiovascular Anesthesiologists was formed, and it has prospered.

Are there negative aspects to subspecialization? Absolutely! You have worked to prove yourself indispensable. Suddenly you are. You have won. Now it is midnight. John Kirkland can't do without you—now you have a problem. Will you cover 24 hours, 7 days a week; will you hire another superspecialist? Other physicians lose skill and expertise in the area. How many call rosters can one department or one group have?

The generalist feels left out; the subspecialist realizes he or she is also uncomfortable in another subspecialty. How many of us are totally comfortable doing anesthesia for open-heart surgery on a 3-kg child? Certainly, resentment may develop early on because a certain elitism develops in any specialty.

Although it is difficult to prove, I believe everyone argues that the patient is the one who benefits from the appropriate subspecialty knowledge. Mortality decreases when the number of identical operations increases at an institution—a fact that explains some of the push toward regionalization and, in addition, gives some basis for the establishment of certain minimum numbers of open-heart cases at an institution. One can argue with the minimum number that is set, perhaps, but not with the concept.

Frequently, teaching departments find that subspecialists teach the specialty itself better because they need to know more about it. As a result the residency program is enhanced. The subspecialist can likewise be a very effective teacher in medical schools, and so academic pressure further subspecialty development. New areas of knowledge and techniques are developed; collaborative efforts develop; papers follow; and promotions come easier. Number of publications does count, probably because a number is easier to document than clinical expertise or teaching ability. Dollars earned is a subject that is not discussable at most schools nor is quality of care. Quality of care requires the faculty to devote time to really take care of patients; faculty members thus have less time for research. In most schools the obvious solution occurs—faculty do not take care of patients, or only do so in private practice. Subspecialization at least tends to counteract that trend, but the fight is tedious and arduous.

Anesthesia and Health Care Costs. For the past twenty years, cardiac surgery and cardiac anesthesia have been very lucrative for both institutions and physicians. Monarchies, even dynasties, of international repute have developed—Cooley and the Texas Heart Institute, Michael DeBakey and Baylor University, Norman Shumway and Stanford, John Kirkland and Alabama, among others. The money was plentiful, and was spread around—cardiologists, surgeons, anesthesiologists, and institutions prospered. We anesthesiologists jumped on the bandwagon of cost-plus medicine: use disposables and pass the costs on to patients; use more monitors, pass the costs on to patients; ventilate patients, pass the cost on to patients; order tests, pass the cost on to patients; do more to be free of medicolegal worries, pass the cost on to patients.

We have caused an explosion in health care costs. Now we are confronted with diagnosis-related groups (DRG's), an oversimplified system, but one that is directed at cutting costs. Suddenly, hospitals make more if doctors do less, use less, order less, do it faster, cut corners. To cope with this new situation requires a total reorganization of our thought processes. We suddenly have to do a balancing act between efficient, cheap medicine and safe medicine. What can be omitted safely and what cannot?

Personnel are a hospital's most expensive commodity. Therefore, we already see a reduction in registered nurses, respiratory therapists, laboratory technicians, and other members of anesthesiologic teams. Low-bid items are a thing of the present and no longer just a joke at teaching hospitals of state universities. Physicians are being scrutinized by hospitals. A physician who has too many outliers may, with luck, first be scolded—but may, on the other hand, be summarily booted off the hospital staff. Hospitals will purchase less equipment and will buy less capital equipment for replacement. The outcome of that scenario is highly predictable.

If you were asked to decrease the cost of anesthesia, what would you do? You might:

- Decrease the cost of halogenated agents by using closed-system anesthesia, perhaps even using only liquid injection techniques. Last year at our institution, we spent $5,000 on halothane, $37,500 on enflurane, and $70,500 on isoflurane.
- Use fewer disposables.
- Use multidose vials.
- Use no or few albumin-containing solutions.
- Use meperidine or morphine rather than sufentanil.
- Work only with fast surgeons.
- Challenge the use of the mass spectrometer to detect esophageal intubations.
- Challenge the use of high-dose steroids in many areas.
- Decrease the use of blood gases.

Of course, the next step on the horizon is the DRG program for physicians. The problems with that program are obvious: who will distribute the payment—the primary care physician (referring physician), the cardiologist, the surgeon, the hospital administrator? Clearly the practice of cardiac anesthesia will change as dramatically in the next fifteen years as it has during the last fifteen.

Although today we naturally think we are on the right course, I thought the same in 1970. It is for us and for the residents of today to recognize that we are just one note in a continuous ongoing symphony. We must look to change, not for change's sake, but for advancement of medical knowledge and to contribute to better care for our patients. In cardiac anesthesia, every day is a challenge, every patient is a heart-lung prep, every patient is one of someone's long series. But we must all remember that every patient is a human being, is an entity, is loved by someone, and has the right to expect every anesthesiologist to follow our own motto: Be vigilant.

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Intraoperative Diagnosis of Myocardial Ischemia

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It is often difficult to diagnose early myocardial ischemia during anesthesia. The electrocardiogram, particularly lead V_5, has become the standard for its intraoperative diagnosis (1). Kaplan and Wells reported that monitoring the pulmonary capillary wedge pressure (PCWP) tracing was useful in the early determination of myocardial ischemia (2). In 55% (10/18) of their patients, an abnormal PCWP waveform was the only manifestation of ischemia. However, the sensitivity and specificity of this technique for the diagnosis of myocardial ischemia remain controversial (3).

Multiple studies now suggest that regional wall motion is the most sensitive indicator of myocardial ischemia (4, 5). Two-dimensional transesophageal echocardiography (TEE) can be used as an excellent monitor of regional wall motion. TEE is a noninvasive ultrasound technique used to visualize the beating heart. An ultrasonic transducer is fitted on a gastroscope housing and positioned in the esophagus behind the heart. Different orientations of the heart can be obtained by rotation of the transducer. The most commonly used views are the long-axis view, with orientation parallel to the long axis of the heart (base to apex), and the short-axis view, where the transducer is rotated 90° from the long-axis position. The long axis is useful in determination of valvular function and regional wall motion and thickening. The short-axis view at the level of the papillary muscles is used for evaluation of regional wall motion, measurement of left ventricular end-diastolic area (ED_a) and end-systolic area (ES_a), and the ejection fraction.

The following case is an example of TEE and PCWP monitoring providing a diagnosis of myocardial ischemia that was not apparent either on lead V_5 of the ECG or on monitoring of radial arterial pressure or central venous pressure.

Case Report

A 74-year-old man, weighing 73 kg, with angiographically documented severe triple-vessel coronary artery disease and normal left ventricular function was admitted to the coronary care unit because of recurrent episodes of angina at rest. His treatment regimen consisted of oxygen by nasal prongs, oral diltiazem, and an intravenous infusion of nitroglycerin at a rate of 30 μg/min. On the morning of surgery, the patient complained of angina and was found to have 3 mm of ST-segment depression in the anterior precordial leads (I, AVL, V_2–V_6). The infusion of nitroglycerin was increased to 60 μg/min, and the pain and ECG changes resolved. The patient was then brought to the cardiac operating room for urgent coronary artery bypass surgery.

Before the induction of anesthesia, ECG leads V_5 and II and radial and pulmonary arterial tracings were obtained. Anesthesia was induced with diazepam, 2.5 mg; fentanyl, 7.3 mg (100 μg/kg); pancuronium, 8 mg; and Metubine, 4 mg, without incident. The nitroglycerin infusion was maintained at 60 μg/min. After endotracheal intubation, a Diasonics two-dimensional transesophageal echocardiographic (TEE) probe was placed, and normal left ventricular wall motion was noted on the short-axis view at the papillary muscle level. The operative course was uneventful until the time of pericardiotomy. At this

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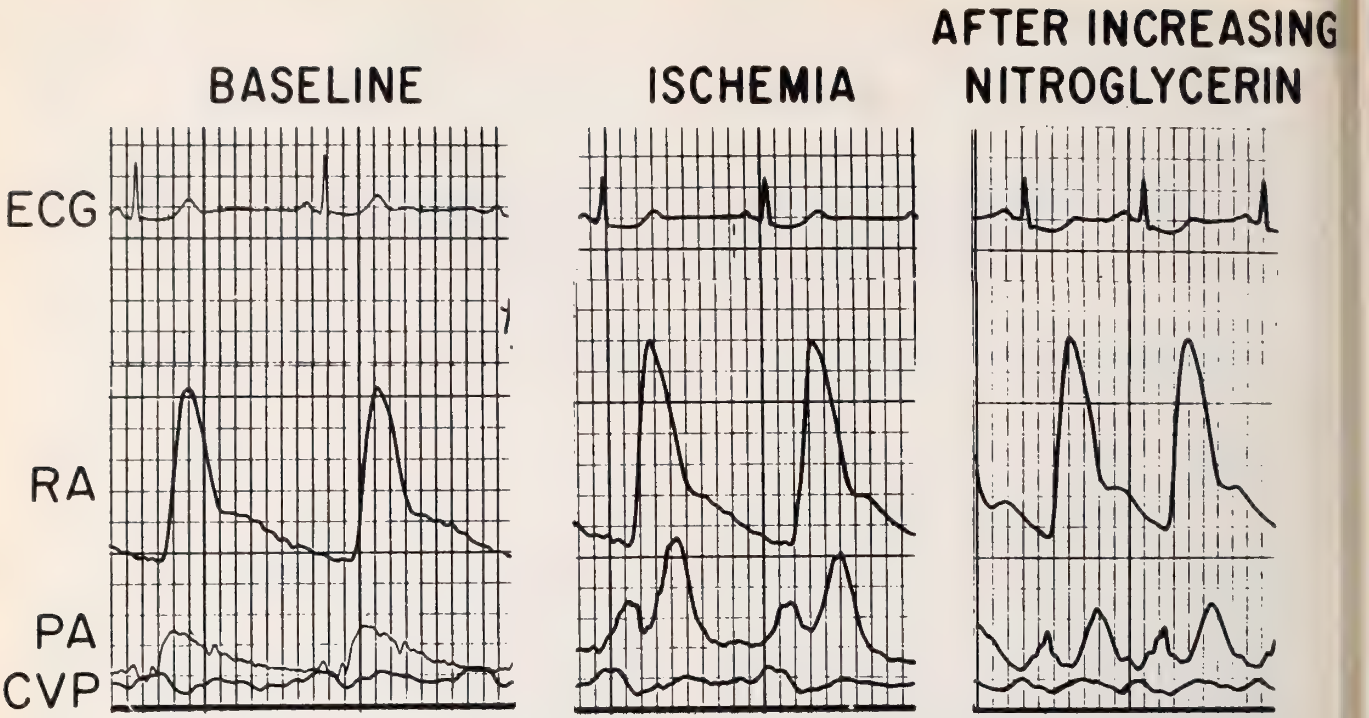

Fig. 1. ECG—calibrated lead V_5. 1 mV = 10 mm. RA, radial artery pressure. In "baseline" frame, PA tracing records pulmonary artery pressure; in "ischemia" and "after increasing nitroglycerin" frames, PA tracing records PCWP. CVP, central venous pressure.

point, despite minimal changes in heart rate, mean arterial pressure, central venous pressure, and ECG leads V_5 and II, "V" waves with a peak pressure of 55 mmHg were first noted on the pulmonary capillary wedge pressure (PCWP) tracing (Fig. 1, Table).

TEE disclosed new left ventricular septal wall hypokinesia and decreased septal thickening, as seen by the treating anesthesiologists and a noninvasive cardiologist (Fig. 2). These findings represented acute septal ischemia. A reduction in the calculated ejection fraction area from 66% to 33% was consistent with this diagnosis. Contrast echocardiography via an injection of agitated saline solution into the left ventricle with simultaneous echocardiographic recording demonstrated no ev-

TABLE

Perioperative Cardiovascular Data

	Preinduction	Postinduction "baseline"	Pericardiotomy "ischemia"	"After increasing nitroglycerin"
Heart rate (beats/min)	62	48	58	57
$\overline{\text{MAP}}$ (mmHg)	71	64	76	72
$\overline{\text{PAP}}$ (mmHg)	18	16	33	30
$\overline{\text{PCWP}}$ (mmHg)	16	13	21	17
Peak "V" wave (mmHg)	18	14	55	25
CVP (mmHg)	8	7	8	7
CO (L/min)	3.70	3.19	3.61	4.37
EF_a*		66%	33%	59%
Regional wall motion abnormality	—	—	+ + + +	+

MAP, Mean Arterial Pressure; PAP, Pulmonary Arterial Pressure; PCWP, Pulmonary Capillary Wedge Pressure; CVP, Central Venous Pressure.

* Ejection fraction area, calculated on a dedicated Diasonics computer by a blinded observer.

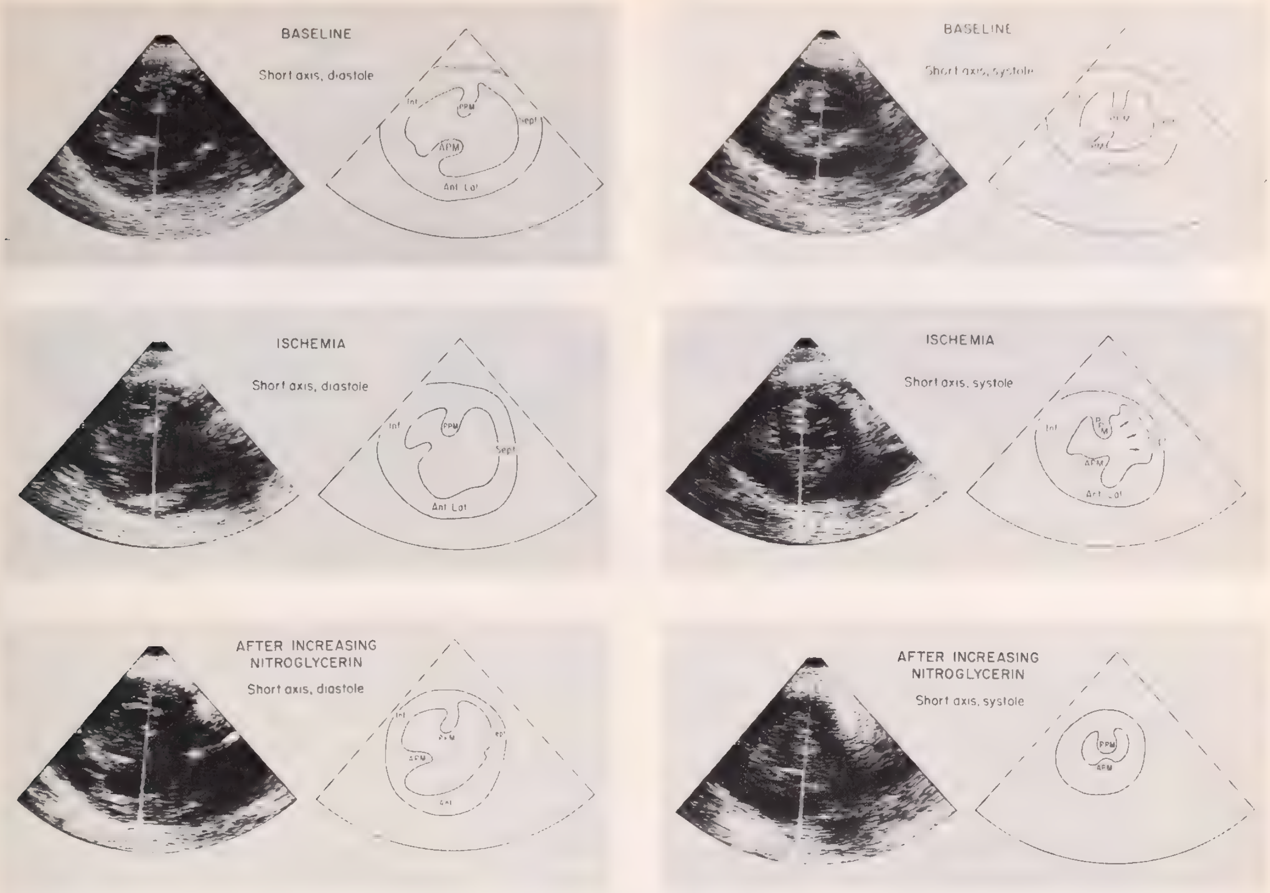
BASELINE
Short axis, diastole
Inf
PPM
APM
Sept
Ant Lat
BASELINE
Short axis, systole
ISCHEMIA
Short axis, diastole
Inf
PPM
Sept
Ant Lat
ISCHEMIA
Short axis, systole
Inf
PPM
APM
Ant Lat
AFTER INCREASING NITROGLYCERIN
Short axis, diastole
Inf
PPM
APM
Sept
Ant
AFTER INCREASING NITROGLYCERIN
Short axis, systole
PPM
APM

Fig. 2. Transesophageal echocardiographic frames on left, idealized interpretations of frames drawn by a noninvasive cardiologist on right. APM, anterior papillary muscle; PPM, posterior papillary muscle; Inf, inferior wall; Ant, anterior wall; Sept, septal wall; Ant-lat, anterior-lateral wall. **Top, left and right** Diastole and systole in baseline state. Note symmetrical contractility and wall thickening. **Center, left and right** Diastole and systole during ischemia. Note area of decreased thickening and hypokinesis of posterior septum indicated by arrows. **Bottom, left and right** Diastole and systole after increasing nitroglycerin. Note return of symmetrical contractility and wall thickening.

idence of mitral regurgitation (Fig. 3) (6). The infusion rate of nitroglycerin was increased to 100 μg/min, and the "V" waves on the PCWP tracing decreased to 25 mmHg. TEE showed resolution of the wall motion abnormality and return of the ejection fraction area to 59%. The patient was placed on cardiopulmonary bypass, and saphenous vein aortocoronary grafting was performed to the left anterior descending, obtuse marginal, and right coronary arteries with endarterectomy of the right coronary artery. After cardiopulmonary bypass, the patient required a brief period of inotropic support with dopamine. Upon completion of the surgery, he was transferred to the coronary care unit with a normal cardiac index, normal wall motion by echocardiography, and no "V" waves on the PCWP tracing. Postoperative ECGs and serial creatine phosphokinase measurements showed no evidence of a perioperative myocardial infarction.

Discussion

Early diagnosis of myocardial ischemia in anesthetized patients is often difficult. The ECG remains the standard method of intraoperative diagnosis. Lead II was monitored initially; then it was shown by Kaplan and King that lead V_5 was a more sensitive indicator of ischemia (1). Experimentally, the ECG is not the most sensitive indicator of early myocardial ischemia. In dogs anesthetized with halothane, Lowenstein et al. showed that the onset of regional wall motion abnormalities was a more sensitive indicator of early myocardial ischemia than the epicardial ECG (4). Similar findings have been reported in man. Using radionuclide angiocardiography, Upton et al (5) and Sugishita et al (7) have reported exercise-induced regional wall motion abnormalities prior to angina or ECG changes. Intraoperatively, transthoracic M-mode (8) and

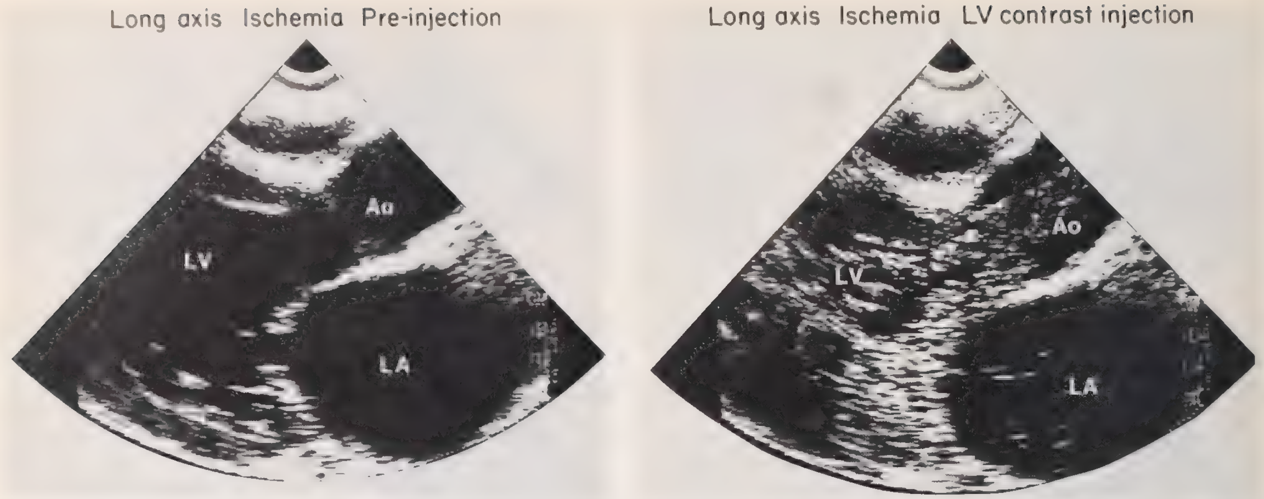
Long axis Ischemia Pre-injection
Ao
LV
LA
Long axis Ischemia LV contrast injection
Ao
LV
LA

Fig. 3. Left Preinjection long-axis view. **Right** Long-axis view during agitated saline contrast injection into left ventricle (LV). Note flow of contrast exclusively through aortic value into aorta (Ao) and absence of contrast flow into left atrium (LA).

two-dimensional TEE (9) techniques have been used to demonstrate significant regional wall motion abnormalities in patients showing only minor ECG changes.

Because of the ECG's limitations, other methods of ischemia diagnosis have been sought. There is a clear correlation between angina and increases in left ventricular end-diastolic pressure or PCWP (10). These increases may be secondary to papillary muscle dysfunction with induced mitral regurgitation (11) or decreased myocardial compliance (12). In the case presented, the contrast echocardiogram revealed no mitral regurgitation, and the "V" waves were due to decreased myocardial compliance. Kaplan and Wells (2) studied the efficacy of pulmonary artery monitoring as a means of diagnosing early myocardial ischemia in anesthetized patients. They concluded that anesthetized and nonanesthetized patients experience similar changes in the PCWP tracing with ischemia, and that the pulmonary artery catheter is useful in the early diagnosis of ischemia.

In summary, we have presented a case of myocardial ischemia in a patient with normal left ventricular function diagnosed by the appearance of a new regional wall motion abnormality and a decreased ejection fraction. As a result of decreased myocardial compliance rather than acute mitral regurgitation, an elevation in the mean pulmonary capillary wedge pressure and the appearance of a large "V" wave were noted. At this time, however, there were no detectable ECG lead V_5 ST-segment or central venous pressure changes. Furthermore, treatment with an increased dose of intravenous nitroglycerin resulted in a resolution of the wall motion abnormality and the return of the PCWP tracing toward baseline. This case demonstrates that even in patients with normal left ventricular function, acute changes in myocardial compliance due to ischemia may be apparent on the PCWP tracing before ECG changes occur. Therefore, either the PCWP tracing or the TEE can be utilized in the early detection of myocardial ischemia in anesthetized patients.

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Monitoring the Left Ventricle: Volume versus Pressure

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The determination of left ventricular volumes is difficult and, therefore, not often included in conventional hemodynamic assessment. This is unfortunate, since numerous studies have demonstrated that cardiac performance can be accurately defined by analysis of the ventricular pressure-volume relationship.

With the development of new imaging technology, the measurement of ventricular volumes has become somewhat more accessible, and it thus seems timely to review how the analysis of the pressure-volume relationship can improve our understanding of cardiac function.

Pressure-Volume Relationship and Cardiac Function

For many years the traditional method for the analysis of cardiac function has evolved around the Frank-Starling mechanism. The Frank-Starling theory is that as myocardial stretch increases, cardiac work increases. The degree of increase depends on the contractile state of the myocardium: the greater the contractility, the higher the left ventricular stroke work.

Closer study of this relationship, however, reveals two problems. First, a change in stroke work can reflect either a change in contractility or a change in afterload. Frank-Starling analysis does not allow one to distinguish between these two variables, although their clinical implications are quite different.

Second, the pulmonary capillary wedge pressure, rather than the left ventricular end-diastolic volume, is often used as an index of myocardial stretch or preload. However, end-diastolic volume and pressure do not necessarily correlate. The lack of correlation has been convincingly demonstrated by Calvin et al (1) in a study of 47 patients in intensive care whose ventricular volumes were determined by radionuclide angiography. In none of the patients could a correlation be established between the left-ventricular end-diastolic volume and the pulmonary capillary wedge pressure.

To study the pressure-volume relationship, a diagram has to be drawn with the left ventricular volume on the horizontal axis and the left ventricular pressure on the vertical axis (2). A single cardiac cycle is represented by a pressure-volume loop. The cycle begins at end-diastole with the isovolumetric phase of the contraction. When the ventricular pressure exceeds the aortic pressure, the aortic valve opens and ejection begins. Diastole starts with the isovolumetric phase of relaxation, followed by the filling phase. Two points on this loop are of particular interest: the end-diastolic point and the end-systolic point.

The end-diastolic point is obtained by the relationship of the end-diastolic volume and end-diastolic pressure. A series of end-diastolic points will define left ventricular compliance. The end-systolic point relates end-systolic volume to end-systolic pressure and can be utilized to define contractility.

By definition, left ventricular compliance equals the change in end-diastolic volume over the change in end-diastolic pressure. Changes in compliance have profound clinical implications. Indeed, if during surgery pulmonary capillary wedge pressure is monitored and a sudden increase in this pressure is noted, it is important to determine whether this increase is due to an increase in end-diastolic volume or a reduction in compliance. A sudden reduction in compliance is diagnostic for ischemia and is often one of the early markers of inadequate coronary perfusion.

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If ventricular compliance were monitored, early detection of myocardial ischemia would become possible.

The second point of interest on the pressure-volume loop is the end-systolic point. In 1974, Suga and Sugawa (3) demonstrated that for a given ventricle all end-systolic points are positioned on a single straight line. This line represents the elastance of the ventricle, which is defined as the change in end-systolic pressure over the change in end-systolic volume. These authors further demonstrated that contractility was directly proportional to elastance. As contractility increases, the elastance slope becomes steeper, whereas it flattens as contractility decreases. The particular value of this index of contractility is that it is independent of changes in preload or afterload.

In addition to defining compliance and contractility, the pressure-volume loop also provides information on cardiac work. Work is by definition equal to the product of pressure and volume. The mechanical work of the heart thus can be derived by calculation of the area within the pressure-volume loop. Whereas the two cardiac cycles depicted in the figure resulted in a similar stroke volume, during the cycle delineated by EFGH that volume was ejected against a higher pressure. The area within loop EFGH is larger than the area within loop ABCD, because more pressure work was performed during the EFGH contraction.

Theoretically, myocardial oxygen consumption should be directly proportional to the mechanical work performed by the myocardium. Experimentally, this is not the case. Indeed, in addition to mechanical work, the heart also performs tensile work, particularly during the isovolumetric phase of relaxation.

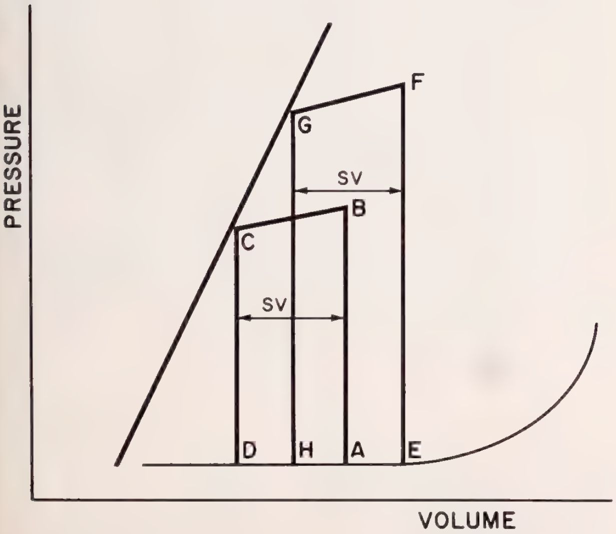

Fig. Two pressure-volume loops, ABCD and EFGH; SV, stroke volume.

In 1982, Suga et al (4) were able to demonstrate that the amount of tensile work performed can be calculated from the triangular area defined by the elastance slope, the descending limb of the pressure-volume loop, and the compliance curve. The total work performed by the heart then is equal to the sum of the triangular area to the left of the pressure-volume loop plus the area of the pressure-volume loop. This total area was shown to be directly proportional to myocardial oxygen consumption. With the construction of pressure-volume loops, one thus obtains information on the compliance, contractility, and global oxygen consumption of the left ventricle.

Current Methods of Volume Measurement

Contrast and Radionuclide Methods. The traditional methods of measuring volume in clinical cardiology rely on either contrast angiography or radionuclide angiocardiography. After the injection of dye or radionuclides, images of the ventricle are obtained, and ventricular volumes can be calculated. Although these two methods are considered to provide the gold standards for volume measurements, they are not easily applicable in the operating room. Not only is the equipment fairly bulky, but the nature of the contrast materials prevents frequent repetition of the measurements. Only two or three injections can be performed at a single session, limiting the value of these techniques for monitoring purposes.

Residual Fractions. A more promising approach is provided by the measurement of residual fraction. In 1951, Bing et al (5) demonstrated that ventricular volumes can be determined from indicator dilution measurements. If a bolus of indicator is injected into the ventricle, a fraction of the indicator will be ejected during the following contraction, while another fraction remains in the ventricle. The remaining or residual fraction will then be diluted by incoming blood, and part of the diluted indicator will be ejected at the next contraction. From the changing indicator concentration, the residual fraction and the ejection fraction can be calculated. The end-diastolic volume is obtained by dividing the stroke volume by the ejection fraction.

Catheters plus Thermistors. Recently, intravascular catheters with fast-response thermistors have been introduced. Using these catheters, Kay et al (6) demonstrated that residual fraction can be measured by injection of thermal indicator. Although the fast-response thermistors were primarily designed for the measurement of right ventricular ejection fraction, they can also be used on the left side of the heart. The indicator is injected in the left atrium and detected in the ascending aorta. These same investigators found a very good correlation ($r = 0.93$) between the left ventricular ejection fraction obtained by this method and first-pass nuclear ejection fraction.

Ultrasound. The final method of volume determination involves the use of ultrasound. Two approaches are possible with this technology.

The first consists of the implantation of ultrasonic microcrystals on the endocardium or epicardium of the left ventricle. The crystals work in pairs: one crystal is an emitting crystal; the other one is a receiving crystal. The time required for the ultrasound to travel from one crystal to the other is directly proportional to the distance between them.

Sodums et al (7) used this technique in awake dogs to measure ventricular volumes and to investigate the influence of various drugs on ventricular contractility. They confirmed that in the control state, all end-systolic points fall on a single elastance slope and that the slope becomes steeper with infusion of inotropes. To define the ventricle, Sodums et al used three pairs of crystals placed at the end points of two perpendicular minor axes and one long axis. A similar but simplified approach using one pair of epicardial microcrystals has been applied in patients by Van Trigt et al (8). These investigators were able to quantify the effects of inotropic agents on myocardial contractility in patients recovering from cardiac surgery, although the measurements involved only a single minor-axis length determination and had to take variations in myocardial thickness into account.

At The Mount Sinai Hospital, left-ventricular volumes have also been measured using direct epicardial two-dimensional echocardiography, as described by Goldman et al (9). Investigations are currently in progress to determine whether this approach provides accurate information on ventricular performance. Left ventricular volumes are estimated from two-dimensional echocardiographic short-axis views and are then correlated with arterial pressure recordings. Preliminary results seem to indicate that elastance slopes can be defined by this method. Unfortunately, data analysis is currently still very time consuming; as a result, contractility information cannot be used for patient care. However, computers for automatic volume determination by two-dimensional echocardiography are under development, and one can therefore hope that the determination of compliance, contractility, and myocardial oxygen consumption by pressure-volume analysis will, in the not too distant future, become routine in the operating room.

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Right Ventricular Function in the Perioperative Period

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Successful diagnostic and therapeutic strategies for evaluation and management of left ventricular dysfunction developed over the last decade have resulted in reduced morbidity and mortality. In contrast, abnormalities in right ventricular function have received scant attention in the scientific literature. Historically, the right ventricle has been viewed as a conduit or reservoir for moving blood from the right side of the heart through the lungs to the left side. Starr and colleagues even cauterized the right ventricle and were unable to find any significant hemodynamic alterations (1). It was not until the work of Donald and Essex, who repeated the study and then altered left ventricular function, that the importance of the right ventricle was understood (2).

The right ventricle is anatomically and physiologically more complex than the left ventricle. In contrast to the left ventricle, which has a relatively simplified mechanism of contraction, the right ventricle contracts via three different mechanisms (3): contraction of the spiral muscles, followed by movement of the free wall toward the intraventricular septum, as the left ventricular contraction causes a "ringer" action. The contraction pattern, as well as the afterload each ventricle faces, results in marked physiologic differences. In comparison to the left ventricle, the right ventricle produces a more gradual increase in pressure as well as a more gradual decline at end systole (Fig. 1). Parallel relationships are also seen in the rate of ventricular outflow. Right ventricular outflow occurs earlier and more gradually and decelerates at midsystole. McFadden and Braunwald have shown that in comparison to the left ventricle, which maintains a constant output over a relatively wide range of afterload, the right ventricle abruptly decreases output with small alterations in afterload (4) (Fig. 2). Conversely, the right ventricle appears to be less preload-dependent than the left ventricle.

Physiological Mechanisms of Ventricular Interdependence. Although the interventricular septum is usually considered functionally part of the left ventricle, Taylor and other investigators have shown the importance of the interaction between left and right ventricle by means of the interventricular septum (5). In a canine preparation with the right ventricle distended (50 ml of blood), aliquots of blood presented to the left ventricle were associated with an increase in pressure in the right ventricle. Similarly, removal of blood from the right ventricle reduced left ventricular pressure. This relationship may have great clinical importance, as defined in the work of Laver and colleagues, who adapted the term "ventricular interference" or ventricular interdependence (6). Ordinarily, increased pulmonary capillary wedge pressure (PCWP) associated with a decreased cardiac output is diagnostic of left ventricular failure. However, under certain conditions, when increased pulmonary artery pressure is present, right ventricular end-diastolic volume and pressure are also increased. This results in a shift of the interventricular septum into the left ventricular cavity. Consequently, increased PCWP and decreased cardiac output (CO) are noted:

$$\begin{tikzcd}
\uparrow \text{PAP} \arrow[r] & \uparrow \text{RVEDV} \arrow[r] & \uparrow \text{RVEDP} \arrow[r] & \text{IVS shift} \arrow[d] \\
\downarrow \text{CO} & \uparrow \text{PCWP} \arrow[l] & \downarrow \text{LVEDV} \arrow[l] & \arrow[l]
\end{tikzcd}$$

(PAP, pulmonary artery pressure; RVEDV, right ventricular end diastolic volume; RVEDP, right

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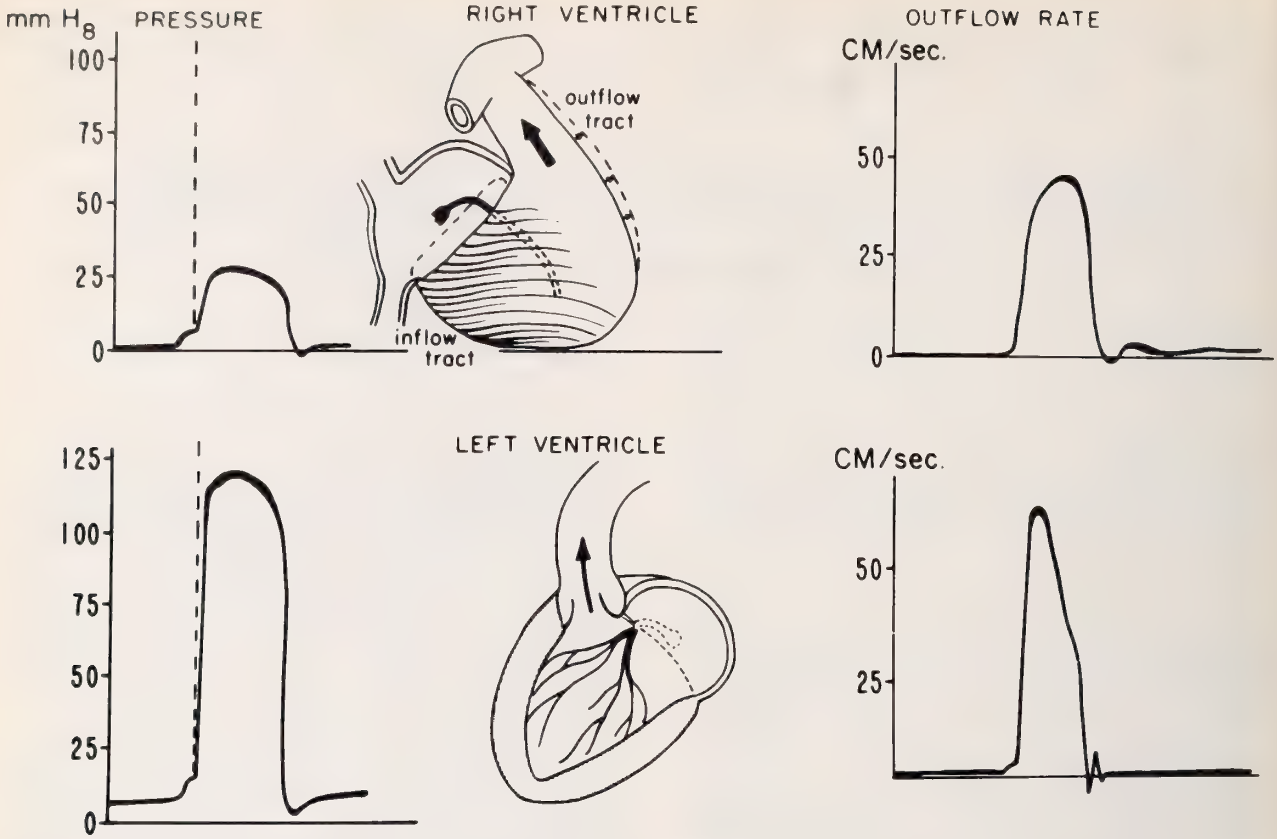

Fig. 1. Comparison of pressure and ejection rate patterns of right and left ventricle. Reproduced, with permission, from Rushmer (3).

ventricular end diastolic pressure; IVS shift, interventricular septum; LVEDV, left ventricular end diastolic volume; PCWP, pulmonary capillary wedge pressure; CO, cardiac output.)

In this particular case, rather than acting in concert with the left ventricle, the intraventricular septum is physiologically associated with the right ventricle. This results in "internal tam-

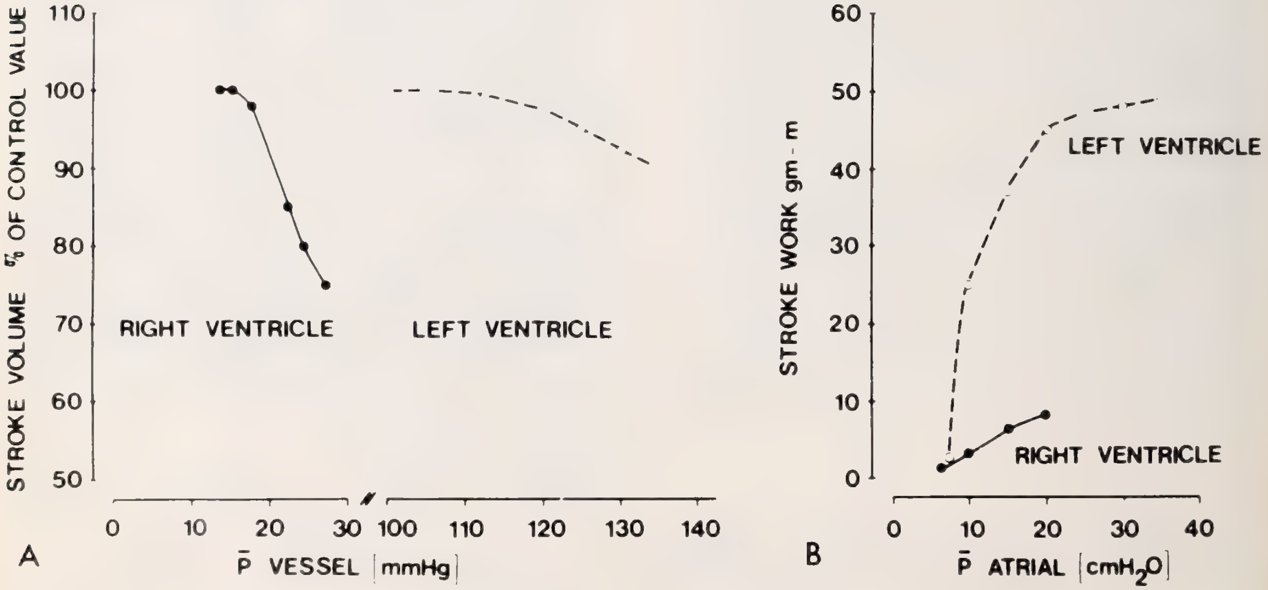

Fig. 2. Varying effects of afterload and preload seen in ventricular function curves from right and left ventricle. Reproduced, with permission, from McFadden and Braunwald (4).

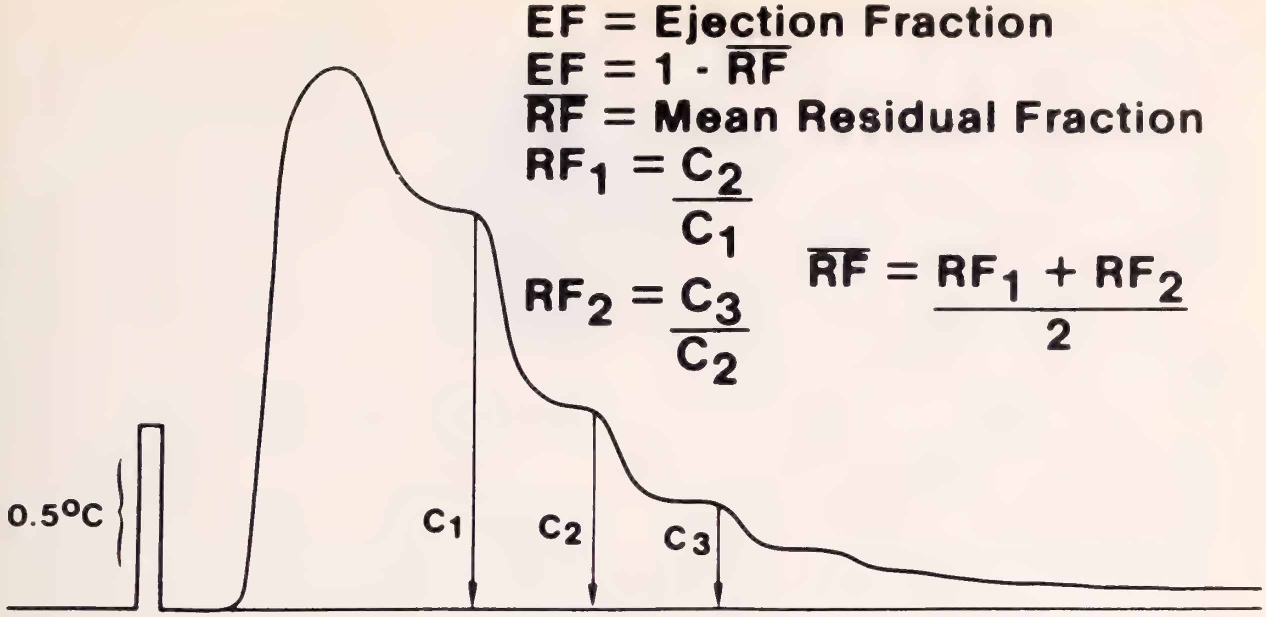

Fig. 3. Thermodilution cardiac output curve obtained with rapid-response pulmonary artery catheter. Following 0.5°C calibration spike, thermal bolus is injected. Plateaus represent diastole. C_1, C_2, and C_3 represent temperature differences between respective diastolic plateaus. RF, residual fraction; EF, ejection fraction. Reproduced, with permission, from Kay et al (11).

ponade." Jardin and colleagues in a clinical study, using two-dimensional echocardiography, showed the importance of this mechanism for reduction in cardiac output in patients receiving positive end-expiratory pressure in an intensive care unit (7).

Ventricular Volume Relationships. Rather than relying entirely on pressure measurements such as PCWP to assess LV performance, recent reports have emphasized the importance of ventricular volume relationships. Calvin et al and Ellis et al, among others, have demonstrated the poor correlation between ventricular end-diastolic volumes and ventricular end-diastolic pressure (8, 9). Although angiography, echocardiography, and radionuclear methods have been employed to measure ventricular volumes, their use is limited in the operating room and the intensive care unit. A system that would allow routine measurement of ventricular volumes, especially on the right side, might enhance diagnostic capability and lead to new therapeutic treatments for right ventricular dysfunction.

Based on indicator dilution techniques, the rapid-response thermistor pulmonary artery flow guided catheter offers great promise (10). Kay and colleagues validated this technique with radionuclear studies in both an animal model and patients after open-heart surgery (11). The thermistor-response time of a standard Swan-Ganz catheter is between 300 and 1,000 msec. When the response time is reduced to 50 msec (rapid-response thermistor), beat-to-beat temperature variations may be seen in the thermodilution cardiac output curve. A typical thermal washout cardiac output curve allows measurement of changes in temperature associated with successive diastolic plateaus (Fig. 3). Computation of right ventricular ejection fraction (RVEF) is then easily accomplished. (Normal RVEF by thermodilution technique is approximately 40%.) RVEF, stroke volume, end-diastolic volume, and end-systolic volume may be easily calculated:

$$\text{Stroke volume} = \frac{\text{Cardiac output}}{\text{Heart rate}}$$

$$\text{End-diastolic volume} = \frac{\text{Stroke volume}}{\text{Ejection fraction}}$$

$$\text{End-systolic volume} = \text{End-diastolic volume} - \text{stroke volume}$$

Thus, from a standard RVEF catheter, the clinician will have knowledge of cardiac output, right ventricular ejection fraction, pulmonary artery and capillary wedge pressure, and right ventricular pressures as well as right atrial pressures (Fig. 4).

Kay et al reported excellent reproducibility and accuracy with this system (11). In a comparison with simultaneous radionuclear RVEF, the thermodilution RVEF measurements were highly correlated (Fig. 5).

Two limitations exist to the thermal indicator technique. In patients with cardiac dysrhyth-

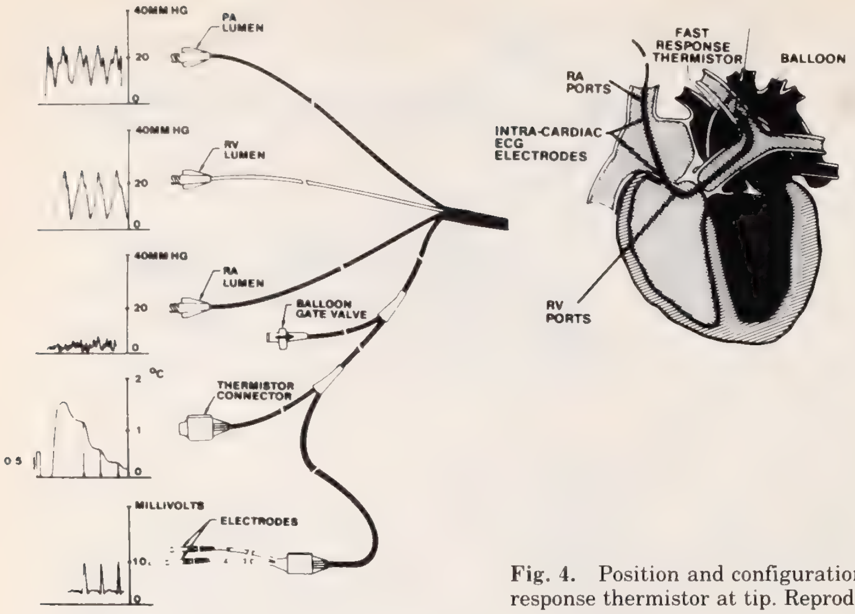

Fig. 4. Position and configuration of pulmonary artery catheter with rapid-response thermistor at tip. Reproduced, with permission, from Kay et al (11).

mias, such as atrial fibrillation, variations in diastolic filling time may introduce error into measurement of RVEF. However, since RVEF is computed with 4–5 beats, an average RVEF may be obtained. Conversely, a beat-to-beat RVEF can be calculated so that minimal and maximal RVEF is known. Second, in patients with regurgitant valvular lesions (tricuspid insufficiency), an erroneous RVEF may be seen, since the technique measures "forward" EF. However, placement of a thermistor in the atrium will allow calculation of regurgitant fraction.

Knowledge of the RVEF may be important in management in a number of patient subgroups. For example, Polak et al recently reported that RVEF was an important descriptor of increased mortality rate in patients who sustained an acute myocardial infarction (12). Patients with an RVEF less than 35% had a markedly increased mortality rate. In an intraoperative investigation, Hines et al evaluated right ventricular function in patients having coronary revascularization (13). Patients with total occlusion of the right coronary artery were at an increased risk for ventricular ischemia, which may escape detection by conventional hemodynamic monitoring methods. Furthermore, improved RVEF was seen after coronary artery bypass surgery.

Potential clinical applications of this technique include measurement of right ventricular function in patients with pulmonary hypertension, right ventricular infarction, and chronic obstructive pulmonary disease and perioperative management of patients undergoing valve surgery, especially of the mitral valve.

In summary, as new scientific focus turns to the right ventricle, the strides made in managing left ventricular dysfunction may be translated to managing dysfunctions of the right side of the heart. In the next few years clinicians will be able to actively diagnose and manage patients who have sustained significant right ventricular dysfunction.

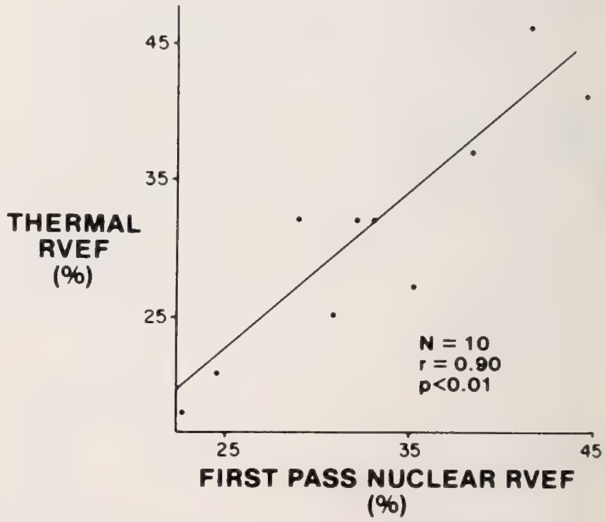

Fig. 5. Correlation between right ventricular ejection fraction (RVEF) by thermodilution and radionuclear techniques. Reproduced, with permission, from Kay et al (11).

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Tetralogy of Fallot: Historical Lessons

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The incidence of congenital heart disease is approximately 8 per 1,000 live births (1). Tetralogy of Fallot, the most common form of cyanotic congenital heart disease (2), accounts for about 10% of congenital cardiac malformations (3). From the clinical and hemodynamic point of view, tetralogy of Fallot is defined by three characteristics (4): first, a large or nonrestrictive ventricular septal defect permitting equalization of pressures between the right and left ventricles; second, right ventricular outflow obstruction sufficient to maintain pulmonary arterial systolic pressure no greater than 35 mmHg, and third, luminal continuity between the right ventricle and pulmonary artery.

In 1944, Blalock and Taussig (5) introduced the anastomosis between the subclavian artery and pulmonary artery as palliative surgery for tetralogy of Fallot. In the mid-1950s, Lillihei attempted total surgical correction by intracardiac repair (6). Surgical techniques evolved rapidly, especially closure of the ventricular septal defect, outflow tract reconstruction, and elimination of surgical damage to the electrical conducting system (7). Since the relative standardization of the surgical techniques, interest has been directed toward the late clinical and hemodynamic results of the operation and the factors that may affect late morbidity and mortality. Our discussion focuses on three important historical aspects of this disorder: the natural history of untreated patients, the early surgical mortality, and the late surgical results.

Lessons from the Natural History of Unoperated-On Patients

Approximately 50% of patients with untreated tetralogy of Fallot die by the age of 5 years (8–11). An additional 25% die by the age of 10 years, and between the ages of 10 and 20 years most have died, so that by the age of 25 only 3%–5% are alive (Fig. 1). The predominant nonsurgical causes of death are approximately evenly distributed between paroxysmal hypoxemic spells, cerebrovascular accident, brain abscess or bacterial endocarditis, pneumonia, and sudden, unexpected death (9, 10). In pregnancy, there is about a 50% incidence of spontaneous abortion, and about 10%–20% of mothers die (10–12).

Polycythemia and high hematocrit may protect the patient from the paroxysmal hypoxemic spells, but such hyperviscosity may lead to thrombotic cerebrovascular accidents. Accordingly, cautious phlebotomics maintaining intermediate hematocrit levels between 60% and 65% have been advocated (10, 13, 14). However, in these cyanotic patients the risk of death is high and constant. Therefore, the historical lesson from natural history studies of unoperated patients with cyanotic tetralogy of Fallot is that surgical intervention early in life should be strongly considered. A similar approach has also been extended to the other operable forms of cyanotic congenital heart disease.

Lessons from the Early Surgical Mortality

When Blalock and Taussig introduced their palliative anastomosis procedure in tetralogy of Falot (5), the early surgical mortality was relatively low and the long-term clinical course of these patients significantly improved (Fig. 1). However, the major breakthrough occurred when in the mid-1950s Lillihei at the University of Minnesota (6) and Kirklin at the Mayo Clinic (7)

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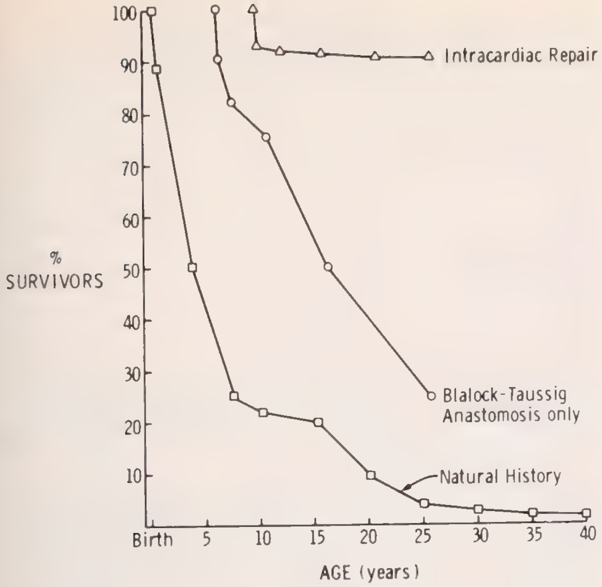

Fig. 1. Natural and surgically modified survival in patients with tetralogy of Fallot. From Garson et al (10).

performed the first intracardiac surgical correction of tetralogy of Fallot. We have had the opportunity to analyze in detail the short- and long-term results of those patients with tetralogy of Fallot who had the earliest intracardiac surgical correction at the Mayo Clinic (4).

The study group comprised 475 patients, 298 male and 177 female, who underwent operation between January 1955 and December 1964. All patients were followed for at least 12 years (or until death, if it occurred less than 12 years postoperatively) and for a maximum of 22 years. Eighty-four patients had primary intracardiac repair within the first 4 years of life and 60 patients between the ages of 20 and 55 years. Before intracardiac repair, 155 patients (33%) had had a previous palliative operation: 121 patients had a Blalock-Taussig anastomosis (5), 27 a Potts-Smith-Gibson anastomosis (15), and 7 a Brock valvotomy or infundibulectomy, or both (16). Three factors contributed to early mortality: years of surgical experience, age of the patient at the time of operation, and residual outflow tract stenosis.

Years of Surgical Experience. Surgical results improved over the years of this study. Thus, the principal factor working against an excellent surgical result in the early patients was the hospital mortality rate, which was 26% in the period from 1955 to 1959 but steadily decreased through the later years (Fig. 2). The higher mortality between 1955 and 1959 was partly due to the surgical production of permanent complete heart block (17). In most experienced surgical centers the operative mortality today is less than 5%. Despite the high hospital mortality of those early days, the courageous experience of these pioneers led to dramatic benefits to patients with tetralogy of Fallot. A similar surgical learning curve has also been observed recently with most of the other complex cardiac surgical conditions.

Age of Patient at Operation. In-hospital or early mortality after total correction was influenced by the age of the patients at the time of operation. Thus, the in-hospital mortality in patients operated on before age 2 years was significantly greater than that in older patients. Therefore, in the late 1960s total correction was not advocated for infants. However, this significantly greater hospital mortality in infants and young children than in older patients may no longer be relevant, given improved operative and postoperative methods, but as pointed out below, it does suggest that the margin for mismanagement may be much narrower in the younger age group.

In the mid-1970s, Barratt-Boyes (18) and Castaneda et al (19) advocated total correction rather than palliation for symptomatic infants with tetralogy of Fallot. They reported that the early and late surgical results were better than with the conventional two-stage repair of early palliation followed by total correction at a later age (18, 19).

Because of concern about the early and late surgical results in these infants, Kirklin (20, 21), Ebert (22), and Shumway (23, 24) in the late 1970s and early 1980s began to advocate an in-

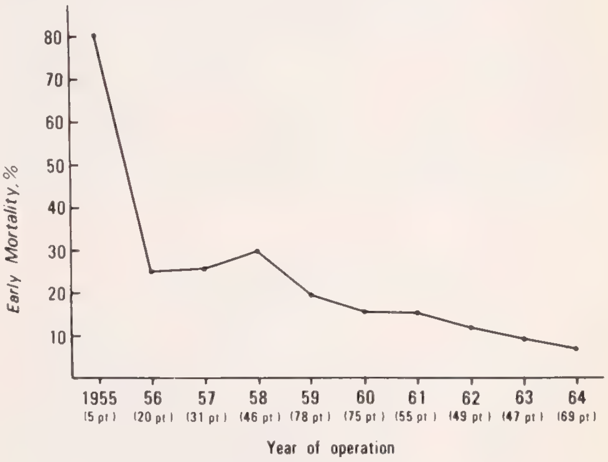

Fig. 2. Hospital or early mortality rates (death within 30 days of operation) of 475 patients subjected to intracardiac repair for tetralogy of Fallot between 1955 and 1964, with long-term follow-up of 12–22 years. Observe improvement in surgical results through the years. Number of patients (pt) operated on each year is noted in parentheses. From Fuster et al (4).

termediate approach. They proposed that total correction in infancy be considered only in very sick infants with hypoxic episodes or severe hypoxemia (0_2 saturation less than 75%). They and others limited surgery to children who had angiographically measured pulmonary arteries of sufficient size, left ventricular end-diastolic volume greater than 60% of normal (25), and an appropriate body surface area. In the absence of these criteria, they recommended that a Blalock-Taussig shunt be placed in infancy, followed by total correction at 4–5 years. This is the treatment of choice today. In less symptomatic patients, primary total correction at age 2–3 seems to be most favorable.

Residual Outflow Tract Stenosis. To calculate residual outflow tract stenosis, intraoperative right ventricular to left ventricular (RV/LV) peak pressure ratio was measured after cardiac repair. The RV/LV pressure ratio was significantly higher for the groups of patients who died in the early postoperative period. Thus, early operative mortality was proportionally related to an RV/LV ratio pressure of 0.65 or greater (Fig. 3). Therefore, if in the operating room after the complete total repair, there is residual pulmonary stenosis with a RV/LV pressure ratio of 0.65 or greater, it is the practice today to resume extracorporeal circulation in order to insert or revise an outflow patch.

Lessons from the Late Surgical Results

The overall late results of this long-term follow-up study are summarized in Table 1. An excellent result, as judged by the patient's being asymptomatic and having no limitation of usual activities, was obtained in 73% of the total group and in 87% of the hospital survivors. Thus far, of 150 female patients with an excellent symptomatic result, 27 have had an uneventful pregnancy and one had a spontaneous abortion. A fair symptomatic result, as indicated by mild to moderate physical limitation, was obtained in 2% of patients. Fourteen patients (3%) underwent reoperation; of these 14 patients, four died at the time of reoperation (21% mortality rate) and one died late postoperatively. The late mortality rate was 6%, most commonly in the form of sudden, unexpected death. The actuarial curves of survival and survival with an excellent result are summarized in Fig. 4. These demonstrate that most problems appear within 2 years of operation, but that thereafter the line is nearly horizontal and comparable with that of the control age- and sex-matched general population.

TABLE 1
Overall Operative Results

Results	Total *n*	Total *%*	1955–1959 *n*	1955–1959 *%*	1960–1964 *n*	1960–1964 *%*
Excellent*	345	73	100	57	245	83
Fair†	10	2	8	4	2	1
Reoperation (alive)	14	3	8	4	6	2
Hospital mortality	79	16	46	26	33	11
Late mortality‡	27	6	17	9	10	3
Total	475	100	179	100	296	100

Adapted from Fuster et al (4).

* On selected catheterization, 11 patients have ventricular septal defect with less than 1.5:1 shunt; five patients have persistent outflow gradient with a right to left ventricular peak pressure ratio higher than 0.65.

† Three patients probably have primary myocardial dysfunction, as judged from the persistent cardiomegaly present preoperatively (no prior anastomotic operation) and lack of postoperative evidence of pulmonary valve incompetence; two patients have significant pulmonary valve incompetence; four have a permanent pacemaker; and one has recurrent supraventricular tachycardia.

‡ Four patients died at the time of reoperation and one patient died 5 years after reoperation.

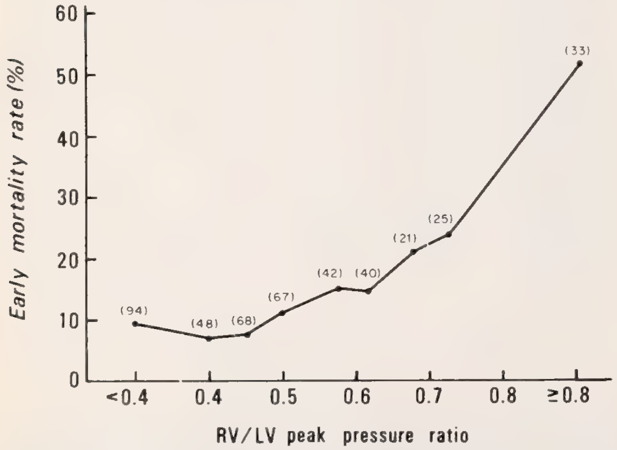

Fig. 3. Relationship between intraoperative right ventricular to left ventricular (RV/LV) peak pressure ratio and early mortality. Observe that ratios of 0.65 or greater were proportionately associated with mortality. Number of patients with each intraoperative ratio is noted in parentheses. From Fuster et al (4).

Thus, 12–22 years after the repair, the majority of the hospital survivors in both the younger and the older age groups had an excellent outcome (4, 26). Some workers report a moderate increase in heart size and a significant incidence of abnormal hemodynamics (27) or reduced cardiac output and heart rate response to exercise (28–1). Yet, when contrasted with the poor life expectancy without operation (10, 11), the operative results are most gratifying.

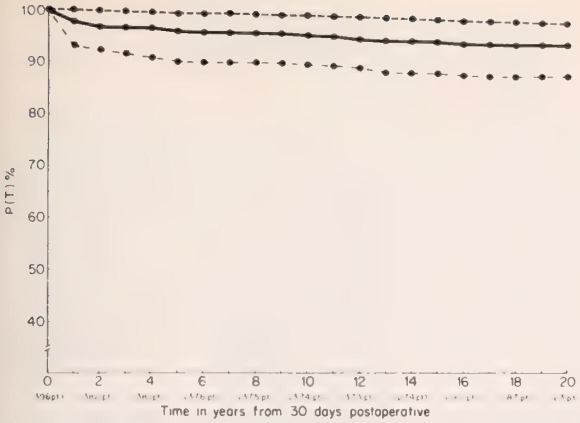

Fig. 4. Probability of deterioration [P(T)] in operative survivors plotted against time in years. Time of deterioration is defined as postoperative year in which late death occurred (middle curve) or in which death, reoperation, or symptoms occurred (bottom curve). Top curve represents control expected survivorship on basis of age and sex distribution, according to Minnesota 1970 white population life table. Number of patients (pt) seen at each follow-up interval is noted in parentheses. From Fuster et al (4).

Two important factors that deserve special consideration are (1) the relationship of electrocardiographic abnormalities, arrhythmias, and heart size to the occurrence of late sudden death and (2) the role of residual pulmonary stenosis versus pulmonary incompetence.

Electrocardiographic Abnormalities, Arrhythmias, Heart Size, and Late Sudden Death. A complete right bundle branch block pattern was found in 85% of the 396 hospital survivors. Seven percent of the patients had additional left-axis deviation (bifascicular block pattern); none of these patients had late sudden death, but one had transient complete atrioventricular (A-V) block at the time of operation. Similarly, no relationship between bifascicular block and late sudden death was apparent in the group operated on from 1965 thorugh 1970 (32). Thus, in contrast with some reports (33–36), our data and those of others (37, 38) do not justify a prognostic electrophysiologic study of the conduction system in postoperative patients with bifascicular block. Yet the relationship of arrhythmias to late sudden death appears to be important and is discussed below. Permanent complete A-V block was observed in 7 (2%) of the 396 patients; three of these patients had late sudden death and, as discussed, this occurred when pacemakers were only in the early stages of development. The four other patients have a permanent pacemaker, implanted in two during surgery and in the other two years later when permanent complete A-V block developed. Transient complete A-V block at the time of operation occurred in 14 (3.5%) of the 396 patients; permanent A-V block developed years later in only two of these, and as mentioned, both required a permanent pacemaker.

Among the 246 hospital survivors who had a follow-up chest roentgenogram, cardiac enlargement, with a cardiothoracic ratio higher than 0.55, was observed in 25% of patients. However, this occurred in 56% of the symptomatic patients and in 62% of the patients who died late of cardiac causes. Of eight patients with late, sudden, unexpected death, six had significant cardiomegaly resulting from a significant ventricular septal defect in three, caused by persistence of preoperative cardiomegaly in two, and without apparent cause in one. Overall, most frequent factors contributing to the postoperative increase in heart size appear to be preoperative cardiomegaly persisting postoperatively (about 33%), significant residual pulmonary valve incompetence (about 25%), and a significant residual ventricular septal defect (about 17%).

Late death is often sudden and usually occurs within the first 2 postoperative years. Continued study is needed to identify causes and to develop methods of reducing the hazard. In this follow-up series, late sudden death occurred in 12 patients (Table 2). Four of these deaths would be unlikely today, because three were related to atrioventricular heart block when pacemakers were still in the earliest stages of development, and one was secondary to pulmonary hypertension resulting from a Potts anastomosis. Sudden death occurred in four patients with residual or recurrent ventricular septal defect, and three of these had significant cardiomegaly. One of these patients had well-documented ventricular tachycardia before death. Of the remaining four patients in whom an anatomic cause of death could not be identified, three had significant cardiomegaly and one

TABLE 2

Late Mortality—Sudden Death

Contributing factor or cause	Patients (*n*)
Heart block (since operation)	2
Heart block (since operation) with fracture of pacer lead	1
Pulmonary vascular disease (previous Potts anastomosis)	1
Ventricular septal defect (residual)	4
Unknown	4
Total	12 (3%)

Adapted from Fuster et al (4).

of them died with well-documented ventricular fibrillation.

It is possible, as other reports suggest (27, 39–41), that most sudden deaths are related to ventricular arrhythmias. Our data also suggest that in many of these patients myocardial dysfunction, as judged from significant cardiomegaly, may trigger the arrhythmia. These observations raise the possibility that follow-up cardiac catheterization to rule out a significant residual structural lesion should be performed in patients after repair of tetralogy of Fallot, particularly in those with significant cardiomegaly. Patients with primary myocardial dysfunction might be subjected to a treadmill stress test and 24-hr Holter electrocardiographic monitoring to identify those who might benefit from antiarrhythmic therapy with Dilantin or Mexiletine (42, 43). However, the incidence of ventricular arrythmias is high in postoperative tetralogy of Fallot (44); perhaps electrophysiologic studies (45) or signal average electrocardiography (46) will identify the high-risk group. Nevertheless, the impact on mortality would be small because sudden, unexplained death, without an underlying anatomic residual defect and presumably related to cardiac arrhythmia, occurred in only four of our patients (0.8%), and a similar low incidence rate (0.9%) was also documented in our more recent patients operated on from 1965 through 1970 (32).

Residual Pulmonary Stenosis versus Pulmonary Incompetence. Thirty-three of the surviving patients who had follow-up cardiac catheterization at least 1 year postoperatively (range 1 to 21 years) and who had no residual ventricular septal defect were evaluated for right ventricular outflow obstruction. The right ventricular to left ventricular (RV/LV) pressure ratio obtained at catheterization was compared with ratios obtained in the operating room after cardiac repair was completed (Fig. 5). In 21 patients with an intraoperative RV/LV pressure ratio of less than 0.65, there was a significant tendency for this ratio to decrease with the years of follow-up in both the group with and the group without an outflow patch; in fact, none of these patients with an intraoperative pressure ratio of less than 0.65 had a ratio greater than 0.52 late postoperatively. In five patients with an outflow patch and an intraoperative RV/LV pressure ratio of 0.65 or greater (Fig. 6), there was a significant tendency for this ratio to decrease with the years of follow-up, although in two patients the ratio was still greater than 0.50. There was no significant average decrease in the elevated RV/LV pressure ratio in the seven patients without an outflow patch, although all of them were asymptomatic. An intraoperative postrepair RV/LV pressure ratio of 0.65 or greater was observed in 16% of the 396 hospital survivors, but did not significantly influence late mortality.

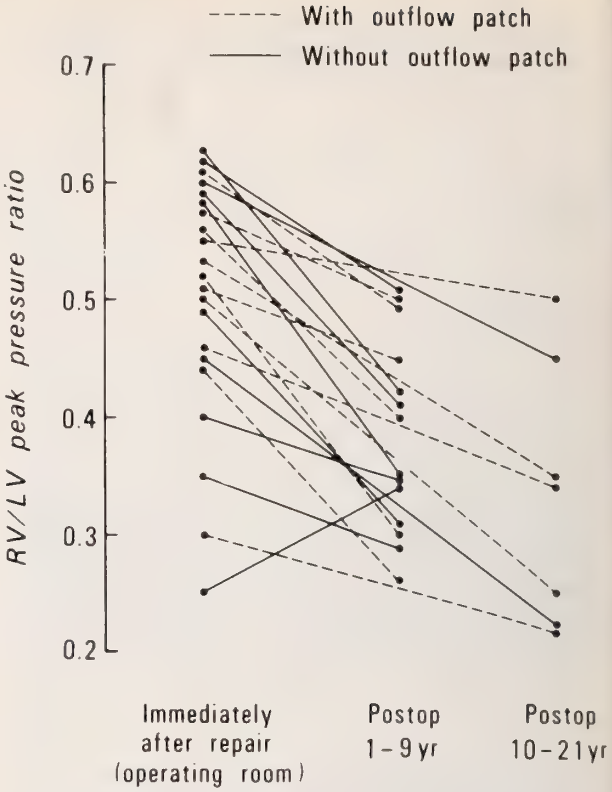

Fig. 5. Right ventricular (RV/LV) peak pressure ratio in 21 patients whose ratio was less than 0.65 immediately after repair (operating room) and who underwent a second hemodynamic study between 1 and 21 years after surgery. With one exception, pressure ratio was lower in second hemodynamic study in all patients. From Fuster et al (4).

The present data suggest that the immediate postrepair RV/LV pressure ratio is usually higher than it will be as the years of follow-up elapse, whether or not a patch reconstruction is used. However, there is a risk in patients in whom an outflow patch is not placed and in whom the immediate postrepair pressure ratio is 0.65 or greater that the pressure ratio will not decrease with time. Moreover, the outflow gradients can increase markedly during exercise (47). Therefore, if in the operating room after the complete total repair without outflow patch, there is a residual RV/LV pressure ratio of 0.65 or greater, extracorporeal circulation should be resumed and an outflow patch inserted.

Over the years, difference of opinion has focused on the ill effects of residual pulmonary ste-

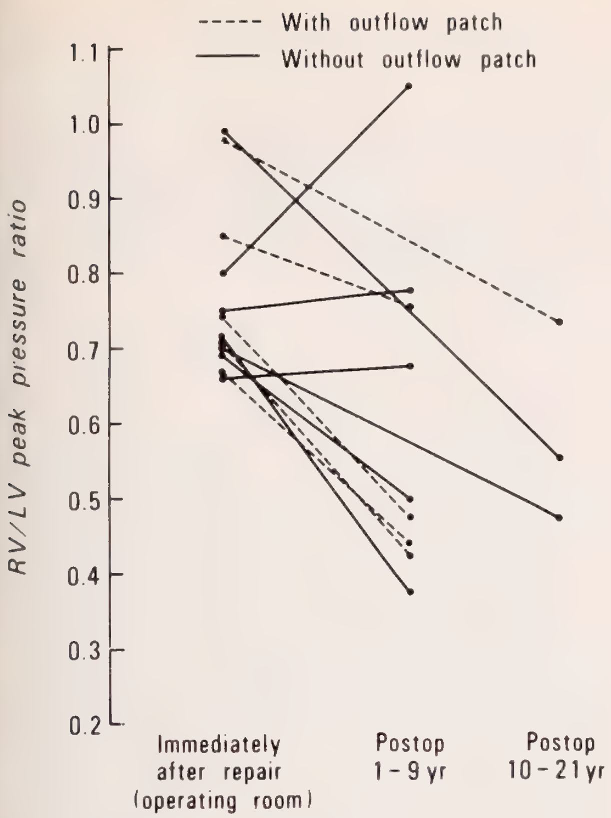

Fig. 6. Right ventricular to left ventricular (RV/LV) peak pressure ratio in 12 patients whose ratio was more than 0.65 immediately after repair (operating room) and who underwent a second hemodynamic study between 1 and 21 years after surgery. In three of the seven patients without an outflow patch, pressure ratio did not decrease. From Fuster et al (4).

nosis versus insufficiency (21, 22, 47, 48). After insertion of an outflow patch across the pulmonary valve annulus, all patients have some degree of pulmonary valve incompetence. Also, some patients who undergo pulmonary valvotomy later manifest pulmonary incompetence. Hemodynamic data indicate that most patients with pulmonary valve incompetence tolerate this lesion well for many years and that their response to exercise remains adequate if there is no significant residual obstruction (49, 50). Indeed, in our long-term study, pulmonary incompetence has contributed to only one late death, to the symptoms of two patients, and probably to the mild increase in heart size of 5% of the 246 patients who had follow-up chest roentgenograms. However, future longer follow-up studies will provide better insight into the long-term significance of such residual chronic pulmonary incompetence. Thus far we do not favor the use of substitute pulmonary valves or outflow tract conduits, except in patients with impaired pulmonary arterial runoff caused by peripheral stenosis, vascular obstructive disease, single pulmonary artery, or agenesis of pulmonary valve with aneurysm of the central pulmonary arteries.

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Deep Hypothermic Circulatory Arrest: Current Status and Future Directions

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Short periods of circulatory arrest, combined with mild to moderate degrees of surface-induced hypothermia to protect the brain, began to be used clinically in the early 1950s (1). The technique became popular but soon was largely replaced by Gibbon's pump oxygenator, which gave the surgeon more intracardiac operating time and extended the surgical domain beyond simple valvotomies and atrial septal repairs to more complex congenital lesions and acquired valvular disease.

However, in the early 1960s the repair of complex congenital heart defects in infants using the pump oxygenator still carried mortality rates in excess of 40% or 50% in the first year of life (2, 3). For these patients, interest in hypothermia with circulatory arrest was revived in the late 1960s by Hikasa (4, 5) in Japan and Mohri (6) in Seattle. These investigators used deep hypothermia with cooling to less than 20°C, combined with up to 1 hr of circulatory arrest, and achieved surprisingly good results in small children. This technique has subsequently been widely used, both with surface cooling and rewarming alone or combined with the pump oxygenator for active cooling and rewarming using perfusion. One recent report of experience with deep hypothermic circulatory arrest (DHCA) in large numbers of children cites mortality of 10% in complex repairs of congenital heart disease during 1979, the most recent year surveyed (7); another report cites 8% mortality during the last 2 years surveyed (8).

DHCA was initially used with surface cooling, but as more experience was gained with the technique, many centers switched to perfusion using cardiopulmonary bypass, thus reducing cooling and rewarming time. As techniques of cardiopulmonary bypass have been refined, early difficulties with extracorporeal circulation in small infants have largely been resolved, permitting use of core cooling with the pump oxygenator for DHCA. A recent study compared surface cooling to core cooling for DHCA and failed to demonstrate any difference in systemic metabolic response to cooling, except for lower blood glucose level with core cooling (9). Studies of acid-base status, oxygen consumption, lactate production, serum electrolytes, and various serum enzymes all showed no difference between the surface-cooled and the core-cooled groups. Total cooling time was only 12 min in the group using extracorporeal circulation for core cooling, as opposed to 64 min in the group using surface cooling. Studies such as this have resulted in the adoption of core cooling using pump perfusion in most centers.

Use in Noncardiac Procedures. Most clinical procedures using DHCA involve the surgical repair of congenital heart defects, although use of the technique has spread to noncardiac procedures for conditions otherwise deemed inoperable. These include complex neurosurgical problems in adults, such as giant cerebral aneurysms and other vascular lesions (10, 11), and tumors involving the inferior vena cava and hepatic veins. Aneurysms of the aortic arch have also been so treated, with good results (12, 13).

Central Nervous System Tolerance

Clinical Studies. As early as 1962 (14) it was determined experimentally in dogs that the brain would tolerate up to 60 min of total ischemia at a brain temperature of 20°C, and this finding has been repeatedly confirmed (15, 16). Throughout the 1970s, 60 min of circulatory arrest at 20°C was the clinically accepted "safe period." Some institutions occasionally extended the time limit

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to 70 min, usually without any obvious postoperative neurologic sequelae. The international clinical experience in thousands of cases generally supports a "safe period" of about 60 min. The incidence of serious postoperative neurologic complications has been low in most of the reported series, approaching that of cardiopulmonary bypass and repair of congenital heart defects without DHCA (7, 8, 17, 18).

Because the technique was apparently so unphysiologic and because the mechanisms of central nervous system protection were poorly understood, the incidence of occasional neurologic problems following DHCA prompted a number of early studies of intellectual functioning after DHCA in children (19, 22). In general, these studies showed that subsequent intellectual function stayed in the normal range in most instances, but a small incidence of late intellectual retardation was seen in most of the series.

Subsequent, more sophisticated studies have shown mixed results. Dickinson and Sambrooks reported a study of 38 children in 1979 (23) that showed a normal IQ distribution up to 6 years following DHCA; no correlation with duration of DHCA was found, and they suggested that 60 min of DHCA was safe. A study from Barratt-Boyes's group in 1980 (24) reported similar results; no correlation between IQ and duration of DHCA up to 70 min was found late postoperatively. Only those patients with preexisting neurologic problems, low birth weight, or low socioeconomic class had a significantly lower IQ than the control group.

In contrast, a study by Wright et al in 1979 (25) suggested a higher incidence of developmental abnormalities after DHCA. This study was supported by a more recent study from England. Wells and associates (26) showed a correlation of IQ difference between siblings and patients with duration of DHCA in the patients; these authors suggested that the safe period was considerably less than 60 min.

Studies of later intellectual development in children following DHCA are difficult to interpret because of the known effects of congestive heart failure and cyanosis in infancy on later IQ, even in the absence of DHCA (27, 28). Comparison of IQ in children with heart disease and in the normal population is thus misleading; a meaningful comparison would require a control group with cardiac disease matched for type and severity of disease with the study group.

Some "hard" evidence to support subclinical damage after extended periods of DHCA comes from a recent Japanese investigation (29). Two of twelve children had abnormal CT scans of the brain one month after DHCA for repair of congenital heart disease. The duration of DHCA was greater than 60 min in both patients with abnormal CT scans, but no patients with DHCA under 60 min had abnormal CT scans. The two children with CT evidence of brain damage showed no clinical evidence of neurologic damage postoperatively. Repeat scans of both children were normal by 11 months after operation.

Experimental Studies. Recent experimental studies have also suggested that there may be cause for concern with circulatory arrest times of about 60 min during deep hypothermia. Treasure and Kirklin et al (30) showed a depression of neurologic function and decrease in numbers of normal neurons when DHCA time in gerbils exceeded 45 min. Another recent study, by Molina et al (31), has suggested that it is deep hypothermia per se which causes morphologic changes in the brain. In this study, microscopic damage appeared equally in all groups of dogs made hypothermic, regardless of whether pulsatile or nonpulsatile perfusion of the head had been continued for 60 min at 18°C or whether perfusion had been stopped for 60 min of circulatory arrest. Earlier investigators also suggested that hypothermia by itself may be damaging to the brain, perhaps by interfering with autoregulation of cerebral blood flow.

However, a number of studies have contradicted this speculation, including a recent study by Fox et al (32). This study, from Kirklin's group at Alabama, showed that in monkeys cooled to 20°C, brain blood flow actually increased as a percentage of total-body blood flow with decrease in perfusion flow rates on bypass. Furthermore, all areas of the brain were equally well perfused, so that autoregulation of brain blood flow appears to extend below previously accepted limits, at least during hypothermia. Thus, problems with gross brain perfusion do not appear to occur during deep hypothermia.

Evidence that levels of profound hypothermia to less than 10°C may cause brain damage and that the safe period is necessarily limited to 60 min or less is disputed by a recent report from Seattle (33). In this study the period of safe DHCA was prolonged to 90 min in dogs cooled to less than 10°C. There was no detectable neurologic injury in the survivors cooled below 10°C, whereas all the survivors of the group cooled to below 20°C showed evidence of neurologic injury after 90 min of circulatory arrest. In an intermediate group cooled below 5°C the incidence of detectable neurologic injury was 35%. This report emphasizes the fact that local institutional practices in mode of cooling, depth of cooling, and perhaps use of adjunctive agents may substantially affect neurologic outcome in infants subjected to DHCA. In addition, it points out the potential for using deeper levels of hypothermia.

All in all, both clinical and experimental evidence suggests that DHCA, as currently used clinically, may cause at least some subclinical brain damage at around 50 or 60 min, and there is better evidence that longer periods, in excess of 70 min, are associated with frank neurologic injury. On the other hand, it seems clear that 45 min or so of DHCA is well tolerated; there are very few suggestions in the literature of significant neurologic damage resulting from this period of DHCA.

Thus, deep hypothermia definitely has a pronounced protective effect on the central nervous system tolerance of total ischemia. However, clinical techniques used for DHCA vary widely among institutions, making it difficult to determine what mechanisms may be responsible for the central nervous system tolerance.

Mechanisms of Protection from Ischemia by Hypothermia

It was long thought that the empirically observed protection from ischemia with hypothermia was due to the decrease in metabolic rate as temperature was lowered. However, studies in several laboratories have demonstrated only a fivefold decrease in cerebral metabolic rate with a decrease in temperature from 37°C to 20°C (15, 16). If the protective effect of hypothermia is related to the reduction in metabolic rate alone, the increase in the safe period of circulatory arrest would be only to 15 or 20 min at 20°C. However, it is clear from numerous studies cited above that the great majority of infants and experimental animals successfully tolerate as much as 60 min of total ischemia at 20°C, a 15- to 20-fold increase in the safe period. Mechanisms other than the decrease in metabolic rate with temperature must be operating to provide this protection during extended periods of total ischemia at deep hypothermic levels.

Reperfusion of the brain after a brief period of circulatory arrest at normothermia results in shutdown of the microcirculation in multifocal areas of the brain, the "no-reflow" lesion, which undoubtedly contributes to the central nervous system damage seen after periods of ischemia. Norwood et al (34) showed that these no-reflow lesions are completely prevented by hypothermia to 20°C, even after circulatory arrest for periods of up to 90 min, and are partially prevented by maintenance of high extracellular pH. These lesions were also shown to be related to anoxia rather than to ischemia alone. Thus, preservation of an intact microcirculation is one way in which hypothermia protects against periods of ischemia.

A subsequent study of tissue levels of high-energy phosphates and pH in perfused rat brain by Norwood et al (35) showed that pH levels in the brain are maintained during ischemia at 20°C, whereas pH falls rapidly to very acidotic levels during normothermic ischemia and does not return to normal levels upon reperfusion. Likewise, in this study, ATP and creatine phosphate levels in brain fell rapidly with normothermic ischemia and did not return to normal levels with reperfusion. In contrast, ATP levels were well maintained during hypothermic ischemia, and although creatine phosphate levels did decline, the decline was not as marked as during normothermic ischemia, and creatine phosphate levels were rapidly regenerated on reperfusion. Since intracellular stores of high-energy phosphates are clearly necessary for maintenance of cellular integrity, the preservation of high-energy phosphates, or at least preservation of the capacity to regenerate high-energy phosphates with reperfusion, is another mechanism by which hypothermia protects the brain during extended periods of ischemia.

The maintenance of tissue pH during hypothermic ischemia in the study by Norwood et al (35) was in direct contrast to the rapid fall of pH during normothermic ischemia. By elevating intracellular pH, hypothermia is thought to preserve the charged state of the intermediary metabolites in the cytosol. These intermediary metabolites are all weak acids whose pH_a is such that they remain in the charged state at physiologic pH. When hydrogen ions accumulate during ischemia and pH falls, these metabolites lose their charge and become un-ionized. As uncharged molecules they are then lipophilic and are thus free to diffuse across the lipid membrane down their concentration gradients. With sufficient depletion of these intermediary metabolic compounds, insufficient concentrations remain in the cell to allow generation of high-energy phosphates during ischemia, or regeneration of stores once reperfusion takes place. In addition, the intracellular enzymes catalyzing these reactions are poisoned by the accumulation of hydrogen ions at their active sites, making the generation of high-energy phosphates doubly hard. Thus the preservation of high intracellular pH by hypothermia during ischemia is linked to the preservation of intracellular stores of high-energy phosphates.

The mechanism by which hypothermia elevates pH in an aqueous cellular environment was elucidated by Rahn et al (36) and subsequently promulgated by White (37) and Swan (38). The neutral pH of water rises as temperature falls; since water is the chief source of hydrogen ions in an aqueous environment, the number of intracellular hydrogen ions will decrease and the intracellular pH will tend to rise during hypothermia as long as the hydrogen ions are adequately buffered. In a closed system during ischemia where no CO_2 exchange takes place, only the tertiary buffering systems are available for this buffering of hydrogen ions. Of these tertiary buffers, neither phosphate nor bicarbonate retains its relative buffering capacity as temperature falls; only the primary protein buffer, the imidazole portion of histidine, does.

The amino acid histidine is abundant intracellularly, and the imidazole portion of this amino acid changes its pK with temperature in a manner parallel to that of the neutral point of water, so that intracellular pH generally rises during hypothermia. The imidazole buffer can maintain these higher intracellular pHs during hypothermia for a relatively long time, even in the face of the anaerobic metabolism which occurs during ischemic conditions. As recently emphasized by White and Swan, to allow the intracellular pH to rise during clinical hypothermia prior to circulatory arrest, it is important to maintain the total CO_2 constant, which means that P_aCO_2 must fall with temperature since HCO_3 increases. Ventilatory support or gas mixtures and flows used in the pump oxygenator must be adjusted accordingly. Failure to appropriately control total CO_2 using P_aCO_2 will result in lowering of pH to levels that are relatively acidotic at low temperature, defeating one of the major mechanisms by which hypothermia protects tissues from ischemia.

Mechanisms of Damage during Ischemia

Imposition of ischemia initiates a chain of events that ultimately leads to cell death when the process is allowed to proceed. These concatenated events include biochemical, functional, and ultrastructual changes. Clearly, from the above work, the biochemical changes are among the first of these events. Structural changes, such as multifocal shutdown of the microcirculation in the brain, appear subsequent to these early biochemical changes.

In the heart as well as in the brain, creatine phosphate and adenosine triphosphate (ATP) fall rapidly and are approximately coincident with functional changes such as changes in myocardial contractility in the heart and neuronal dysfunction in the brain. At normothermia these changes remain reversible for about 3 or 4 min in the brain and about 20 min in the heart. From the work cited above, it is clear that during hypothermia the chain of events leading to cell death can be reversed at up to 60 min in the case of the brain and substantially longer in the case of the heart.

The changes in pH and high-energy phosphates and, on a multicellular level, changes in the microcirculation that result from ischemia are also in part responsible for furthering the linked chain of events that leads to irreversible cellular damage. Recent work on calcium flux in the cell has suggested another mechanism of ischemic damage. During normothermic ischemia or during normothermic perfusion with calcium-free solutions, calcium channels in myocardial and neuronal cell membranes appear to open, perhaps because some of these channels are voltage sensitive and cells tend to depolarize during ischemia as lowered ATP stores lead to decreased activity of the Na-K membrane pump.

As a result of the opening of the calcium channels, reperfusion of the normothermic ischemic cell with calcium-containing solutions, that is, blood, leads to a massive influx of calcium into the cell, termed the "calcium paradox" (39). This massive influx of calcium leads to irreversible structural damage in cells, including tissue disruption due to contracture and release of intracellular enzymes. This has been shown to be the basis of what is called the "stone heart" and has also been associated with damage in neuronal cells. Hypothermia to 18°C has been shown to totally prevent membrane damage from the calcium paradox phenomenon and thus calcium influx on reperfusion (40). The mechanism of this protection appears to be a phase transition in the membrane lipids (from a more liquid to a less liquid state) that stabilizes the membrane structure (41).

Recent work has shown that blocking calcium entry during anoxia by using calcium-free perfusate allows complete recovery in populations of neuronal cells in vivo (42). Blocking calcium entry using cobalt to block Ca^{2+} channels was also effective in protecting neurons against anoxia at 37°C, so that calcium influx during anoxic perfusion or during reperfusion after total circulatory arrest probably plays a large role in brain damage with ischemia. A similar prevention of calcium influx is one way in which hypothermia prevents ischemic damage. This calcium influx is also probably important in ischemic heart damage as well and seems to be critical in "reperfusion injury."

The hypothesis that prevention of calcium entry will protect against ischemic damage of the brain was recently tested in an intact animal by Michenfelder's group at the Mayo Clinic (43). Using a nimodipine infusion after 17 min of normothermic brain ischemia in monkeys, they were able to show marked improvement in neurologic outcome in treated monkeys compared to control monkeys. Nimodipine is a calcium channel blocker that is relatively specific for the brain; thus with prevention of Ca^{2+} influx into neuronal cells during reperfusion, neuronal integrity is better preserved.

Future Directions

Understanding of the mechanisms of the ischemic protection afforded by hypothermia has many potential applications in myocardial ischemia and cerebral ischemia during normothermic clinical conditions, since the mechanisms of ischemic damage seem to be similar regardless of temperature. Because damage occurs much less rapidly during deep hypothermia and appears to be more easily reversible, study of these mechanisms of damage during hypothermia is much easier. The observation that hypothermia prevents the damage associated with Ca^{2+} influx, for example, suggests the possible use of calcium channel blockers in the treatment of cerebral ischemic events, as in the experimental study by Newburg et al. (43).

One hopes that further understanding of the physiology underlying more profound hypothermic levels of hypothermia, to 10°C or even lower, will in the future permit safer use of DHCA. Clinical use of deeper levels of hypothermia may permit extension of the "safe period" to 90 min or even longer.

With increasing understanding of phenomena such as ischemic depletion of high-energy phosphates, calcium influx upon reperfusion, and pH changes with temperature, pharmacologic and physiologic interventions such as use of calcium channel blockers upon reperfusion, manipulation of electrolytes in reperfusion solutions, and rational use of various agents in "plegic" solutions for both the heart and the brain may become possible. These advances await extension of our current fragmentary knowledge of the cellular physiology of hypothermia and ischemia. Since during DHCA we are really dealing with a reversible form of "cell death," research in this area should have wide application to fundamental problems in medicine.

Summary

Although deep hypothermia with circulatory arrest has been used clinically for about thirty years, its safety and its proper role in the armamentarium of the surgeon are still controversial. Disagreement focuses on the "safe period" of circulatory arrest, defined as central nervous system tolerance of the period of ischemia without subsequent neurologic dysfunction. Although major neurologic problems following DHCA are infrequent, some recent studies of subtle indicators of cerebral damage, such as intelligence quotient, have suggested that extended periods of deep hypothermic circulatory arrest in infancy may limit later intellectual development.

The controversy continues because the mechanisms by which hypothermia protects the brain against circulatory arrest are incompletely understood. These mechanisms include maintenance of cerebral microcirculation, high tissue pH levels, and intracellular high energy phosphates in cerebral tissue and prevention of massive Ca^{2+} intracellular influx during ischemia and reperfusion.

Knowledge of the physiology underlying DHCA is scanty. Extensive investigation of the cellular physiology of hypothermia is required before present empiric techniques of DHCA can be improved. Possible areas of improvement include optimal pH management during hypothermia, use of lower temperatures, prevention of Ca^{2+} influx during ischemia and reperfusion, and use of protective agents such as calcium channel blockers prior to and after arrest.

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Mechanical Support of the Failing Heart

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Low-cardiac-output syndrome continues to be a significant cause of morbidity and mortality in cardiac patients, even after three decades of progress in cardiology, pharmacology, anesthesia, cardiac surgery, and postoperative care. Why? Perhaps because sicker and older groups of patients are undergoing cardiac surgery, coronary angiography, angioplasty, and major noncardiac operative procedures.

Acute myocardial pump failure is seen in patients suffering acute myocardial infarction, or cardiogenic shock or following open-heart surgery when it is impossible to wean patients from cardiopulmonary bypass. Patients with chronic myocardial pump failure usually have progressive cardiomyopathy or chronic congestive disease of several etiologies. Advances in pharmacologic and other therapies, including pacing, do not always provide adequate improvement in there patients.

For these reasons, a number of mechanical techniques to assist myocardial function have been developed and clinically used (Table) as preventive and therapeutic measures or as a last resort for salvaging the patient in extreme circumstances.

External Cardiac Massage. The introduction of closed-chest cardiac massage (1) has provided some realistic hope for prevention of the nearly 1,000 prehospital-admission sudden deaths per day that occur in the United States (2). This simple mechanical technique is commonly used as a first step in cardiopulmonary emergency resuscitation.

External Counterpulsation. External counterpulsation is a noninvasive technique for augmenting the central circulation. The extremities are placed in a hydraulic system, and synchronized compression, triggered by the electrocardiogram, may improve hemodynamic status. The physiology, indications, and current results were recently summarized (3).

Pacemaker. The history, current status, and future possibilities of the use of pacemakers have been widely reported on (4, 5). Computer techniques for electrostimulation of myocardium, rate-responsive pacing, and extension of electrostimulation to the control of tachydysrhythmia and fibrillation are among the new uses of pacemakers (6).

Intraaortic Balloon Counterpulsation. In the early 1960s the concept of counterpulsation with an intraaortic balloon pump was introduced. The balloon is positioned in the descending aorta, just distal to the left subclavian artery. The device was used only a few times in terminal clinical situations, and there were no survivors (7). It was not until 15 years later that the concept of intraaortic balloon counterpulsation started to be routinely used in patients with postcardiotomy circulatory insufficiency (8); during 1976–1977, more than 5,000 patients received treated support (9). The mechanism of counterpulsation is a diastolic increase of systemic organ perfusion resulting from higher mean arterial pressure and diastolic augmentation of coronary blood flow.

This system is popular because it offers simplicity of deployment, safety, and predictability of effect. It is portable, allows easy insertion at the bedside, emergency room, or cardiac catheterization laboratory, and may be used for prolonged periods with minimal complications (8). Since 1978 percutaneous insertion of the balloon using disposable kits has become popular; this method of placement reduces delays in deployment in acute cardiogenic shock (10). The simple technique for percutaneous placement via the femoral artery allows insertion in urgent situations by cardiologists, internists, anesthesiologists, and

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TABLE
Mechanical Support of the Failing Heart

External cardiac massage (1, 2)
External counterpulsation (3)
Pacemaker (4–6)
Intraaortic balloon counterpulsation (7–10)
Femorofemoral bypass (11)
Left-heart assist device (12–27)
Intrapulmonary balloon counterpulsation (30)
Right-heart assist device (28, 29, 31)
Biventricular heart assist device (24)
Total artificial heart (32–36)

other physicians (after appropriate training), when a cardiac or vascular surgeon is not available.

The technique is used in the following situations:

Cardiac pump failure, which includes cardiogenic shock secondary to the myocardial infarction; failure to wean the patient from conventional cardiopulmonary bypass after open-heart surgery; and low-cardiac-output syndrome postoperatively after acute noncardiac procedures.

Stabilizing patients for coronary angiography, induction of anesthesia, and cardiac surgery for preinfarction angina, massive myocardial infarction, and complications of acute myocardial infarct (ventricular septal defect, left ventricular aneurysm, or mitral regurgitation).

In conjunction with high-risk percutaneous transluminal coronary angioplasty or thrombolytic therapy.

In emergency major noncardiac surgery for patients who have hemodynamic unstable angina or left main coronary disease or who have had myocardial infarct.

Femorofemoral Bypass. Femorofemoral bypass has been used for the temporary treatment of cardiac failure, and support was continued with intraaortic balloon counterpulsation as a final resort to salvage the life of patients with extremely low cardiac output or after resuscitation following cardiac arrest (11). The femorofemoral bypass has been used in a variety of clinical situations (massive pulmonary emboli, cardiogenic shock), but the described techniques required heparinization, and cardiac decompression could not be achieved with a closed chest.

Left-Heart Assist Device. A simple method to assist the left side of the heart temporarily has been used clinically at The Mount Sinai Medical Center in New York (12, 13). The system consists of a roller pump connected to a pair of specially designed obturated cannulae (Fig. 1). This system has an important advantage over similar devices (14). Discontinuation of support does not require general anesthesia and thoracic reentry, a significant risk in the patients for whom the device is useful.

The system is designed for implantation via a thoracic approach when it is impossible to wean a patient from cardiopulmonary bypass owing to low-cardiac-output syndrome despite other pharmacologic and mechanical interventions following cardiac surgery.

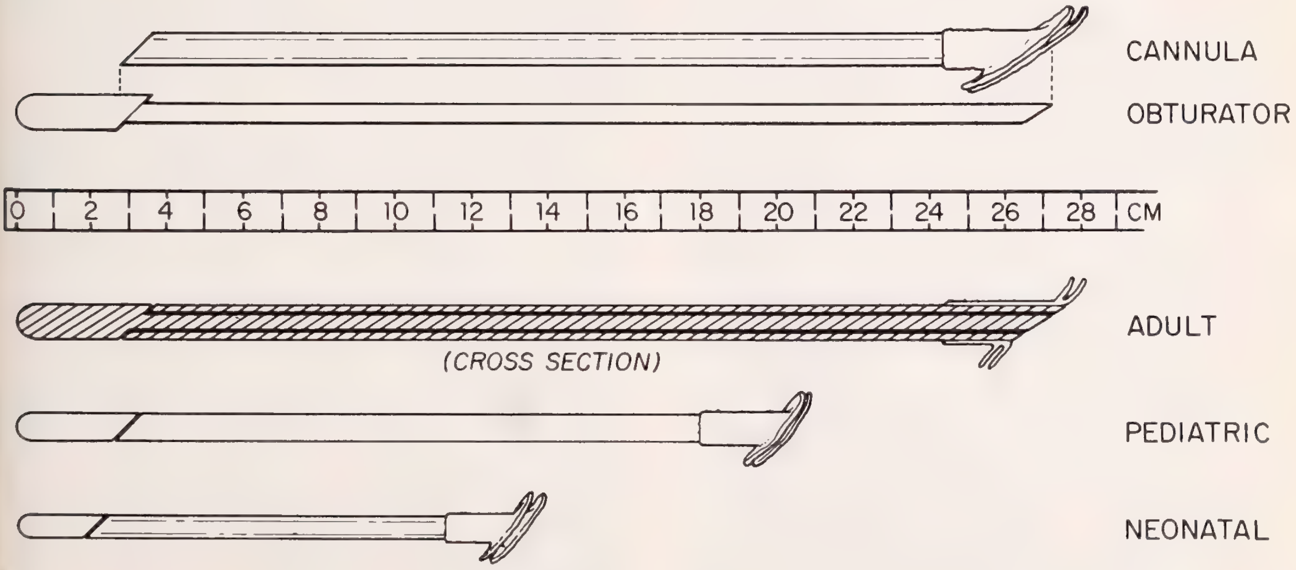

Fig. 1. Obturated cannulae (Kontron Cardiovascular Inc., Everett, Massachusetts) used to assist the left side of the heart at The Mount Sinai Medical Center.

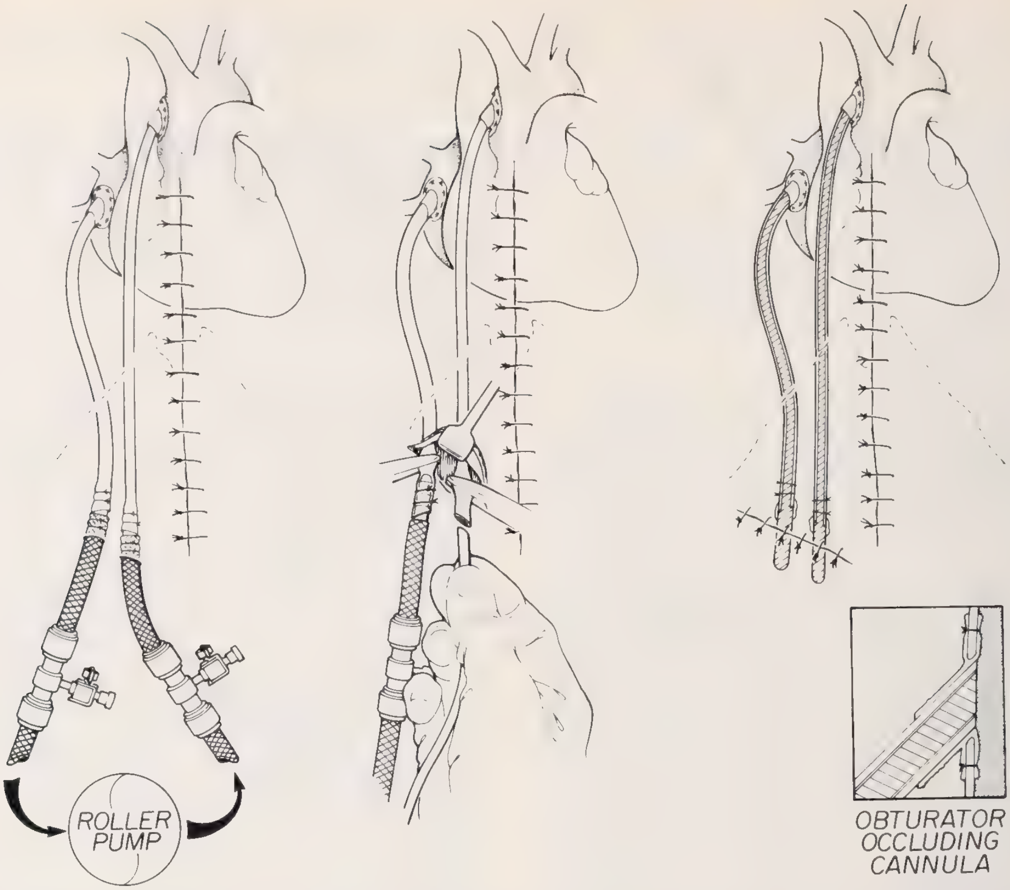

Fig. 2. Cannulae anastomosed to the left atrium and aorta and connected to an external roller pump (left). Insertion of obturator in aortic cannula following discontinuance of left-heart assist (center). Obturated cannulae sealed and implanted subcutaneously (right).

The cannulae are anastamosed to the left atrium and aorta (Fig. 2). The distal ends lead subcutaneously to exit in the right upper quadrant of the abdominal wall and thence connect to the roller pump tubing. Conventional cardiopulmonary bypass is gradually discontinued as the device is brought into use. Sternal closure is carried out and the patient is transferred to the intensive care unit while the device (and intraaortic balloon counterpulsation if that treatment is deployed) is operated on battery power. The flow rate of the device is adjusted so that the combined output of the patient's left ventricle and the device is at least 2.5 L/min/M^2 of body surface area. Separation from the device is considered when the device flow is 500 ml/min with stable systemic and left atrial pressures. At separation the distal ends of the cannulae are exposed under local anesthesia, the pump is turned off, the tubing disconnected, and an obturator inserted into each cannula lumen (Fig. 2). The obturated cannula ends are buried subcutaneously, and the skin is closed (Fig. 2).

Among 27 patients, 21 days was the longest period of operation of the device. Eighteen of the twenty-seven patients were separated from the device, and nine were subsequently discharged from the hospital. The patients who retained the obturated cannulae have tolerated them well. Technical details and results have been previously described (15–18).

Many other, more complex temporary devices to support the left side of the heart are available for implantation in the abdomen (22, 23). For biventricular postoperative heart failure, paracorporeal artificial ventricles for left and right pumping are used (24).

With such temporary devices, we can expect improvement in myocardial tissue that is reversibly damaged owing to surgical trauma, edema, or metabolic dysfunction. Additional theoretical considerations for temporary assistance of the heart include the use of support to gain time for transportation of the patient to a site where definitive operative correction, including cardiac transplantation or implantation of a total artificial heart, can be performed.

Another development is the permanent auxiliary ventricle (25, 26). This device is designed to improve the living conditions of patients with chronic heart failure who are not qualified for other devices or heart transplantation.

Right-Heart Assist Device. Mechanical support of the failing right ventricle has been reported by a number of investigators using extracorporeal membrane oxygenators for venoarterial bypass (28, 29). Recently, support by intrapulmonary balloon counterpulsation was used clinically (30). A review of the right-heart support, including technical considerations and results, has recently been published (31).

Total Artificial Heart. In patients with terminal chronic heart failure the only hope is implantation of a total artificial heart or a heart transplantation. Since 1957, 247 scientists have been working under the direction of Dr. Kolff to develop, and have been credited by him for developing the artificial heart implanted in the first human recipient in Utah (32). Similar efforts to develop an artificial heart have been made and are continuing in many other centers around the world. In 1982 the Jarvik 7 Total Artificial Heart was approved for clinical trial in the United States. The artificial heart is pneumatically driven through a pair of tubes connected to a bedside or a portable power device (33).

Dr. Barney Clark, a 61-year-old dentist suffering from terminal heart failure due to idiopathic cardiomyopathy, was not qualified for any heart transplantation program in the United States. On December 2, 1982 his native heart was replaced by the total artificial heart (34). The surgical team was led by DeVries; the anesthesiologist was Pace (35). The surgery started as an emergency owing to deterioration of the patient's condition. The patient was not premedicated. In the operating room, a monitoring line was established. Fentanyl was used for anesthesia and metocurine as muscle relaxant. The patient was intubated and ventilated with oxygen. During bypass, the anesthesia was supplemented with isoflurane. The operative procedure took nearly 8 hr, and the patient was on cardiopulmonary bypass for more than 4 hr. Technical problems with the artificial heart led to two subsequent operations.

Dr. Clark had good days and bad days. He experienced severe complications, and his death, 112 days after operation, raised a number of difficult questions (35). However, Dr. Clark's operation must be considered a remarkable accomplishment. DeVries has implanted two other total artificial hearts in patients in Louisville, Kentucky (personal communication).

In September 1984, the Stanford University group implanted an artificial pump into a dying patient who was waiting for an appropriate heart donor. An electrically driven artificial heart supported the patient's circulation for several days until a suitable heart with acceptable tissue match was available for transplant. The homologous heart transplant was successful (A. K. Ream, personal communication).

Ethical considerations of limited recovery or survival with dependency on an artificial device involve issues concerning the quality of life and dignity in dying. These complex moral and economic issues affect not only the patient and the family, but the medical community and of course the general public. In the coming decade both the ethical and the technical problems associated with mechanical support of the failing heart will, one hopes, be resolved.

Many hundreds of investigators have contributed to the field of mechanical support of the failing heart, only a handful of whom are cited here for reasons of space; progress so far is the result of the successful collaboration of this myriad of researchers.

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Beta-Adrenergic Blocking Agents: Review and Update

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Beta-adrenergic blocking agents are now used to treat a wide spectrum of clinical disorders. The earliest indications for beta blockers were strictly cardiovascular—hypertension, angina pectoris, and supraventricular arrhythmias. More recently their use has been considerably extended for both cardiac and noncardiac conditions to include thyrotoxicosis, hypertrophic cardiomyopathy, migraine, glaucoma, myocardial infarction, and gastrointestinal bleeding (1, 2). Furthermore, the availability of agents with selectivity for subgroups of beta receptors, partial agonist activity, and additional alpha-adrenergic blocking actions has made the use of these agents possible in even larger numbers of patients.

Developed by Black and co-workers in the 1960s, propranolol was the first clinical beta blocker. Over the years one after another was added, so that now nearly 20 agents of this type are available worldwide; eight of these are presently approved in the United States. This brief review concentrates on clinically important uses of and differences among these drugs.

Actions of Beta Blockers

Catecholamines mediate multiple physiologic and metabolic responses. The catecholamine-receptor complex activates the enzyme adenyl cyclase, located on the plasma membrane. Activated adenyl cyclase increases formation of cyclic AMP, which in turn inhibits or stimulates several physiologic or metabolic processes (3).

Adrenergic blockers (antagonists) are agents that interact with the receptor, but cause no response, while preventing the action of agonists (catecholamines). They thus exert their effects via competitive inhibition. Two types of adrenergic receptors exist, and antagonist drugs may be divided into those with affinity for alpha receptors, such as phentolamine, or with primarily beta-receptor blocking activity, such as propranolol (4).

All the beta blockers presently in use have characteristic and fundamental actions on heart rate, cardiac output, and blood pressure. Beyond this a number of subtle and not so subtle differences exist between them. These differences relate to the following characteristics: cardioselectivity, membrane-stabilizing activity, intrinsic sympathomimetic activity (ISA), and lipid versus water solubility.

The most important effects of beta-adrenergic blocking agents are on the cardiovascular system, primarily the heart. These effects include reduction in heart rate, cardiac output, and blood pressure. The effects on cardiac output and heart rate are more dramatic during exercise. Other effects include constriction of smooth muscle in bronchi and arterioles. In skeletal muscle these agents inhibit the activity of the sodium-potassium pump, among other effects.

Individual Characteristics of Drugs

Cardioselectivity. Beta receptors have been subdivided into two discrete subgroups, beta-1 and beta-2. Each of these mediates different physiologic and metabolic responses (4). Beta-1 receptors are present primarily in the heart and also promote renin secretion. Beta-2 receptors predominate in other regions: bronchi, peripheral arteries, the gastrointestinal system, and skeletal muscle. Activation of beta-2 receptors results in bronchodilatation and vasodilatation; therefore,

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beta blockade may cause bronchoconstriction and vasoconstriction (5). The effects of beta-2 blockade are of little clinical significance in normal persons, but in asthmatics and patients with peripheral vascular disease they may be severe (6).

Selective beta-1 blockade, therefore, slows the heart rate, is negatively inotropic, and modulates elevated blood pressure. However, it should not cause bronchospasm or peripheral vasoconstriction, and beta-1 selective blockers are considered usable in patients with obstructive lung disease or peripheral vascular disease (though beta-1-induced lowering of cardiac output may aggravate the latter).

However, although cardioselective beta blockers are used in such situations, one must add an important qualification. Pharmacologic specificity is never complete. Cardioselective beta blockers have only a relative and not an absolute ability to spare beta-2 receptors. In fact, their selectivity exists only in lower dosages. In higher doses the distinctions are blurred, and beta-1-"selective" blockers also block bronchial, vascular, and other beta-2 receptors (3). Thus, although beta-1-selective agents are preferable to the others in patients with obstructive pulmonary disease and peripheral vascular disease, these agents should still be used with caution, since even "selective" beta-1 blockers may aggravate bronchospasm in certain patients. In patients with active bronchospastic disease, they should be avoided entirely (6).

Recently another point about selective versus nonselective beta blockade has been made. Catecholamines cause hypokalemia (via stimulation of the sodium-potassium pump in peripheral tissues). Nonselective agents block this effect and therefore block catecholamine-induced hypokalemia. Selective agents may not block this hypokalemic response. Although this difference is of interest, its clinical significance is yet to be determined.

Metoprolol, atenolol, and acebutolol are the currently available cardioselective beta blockers.

Membrane-Stabilizing Activity. Certain beta blockers have a quinidinelike membrane stabilizing effect on the cardiac action potential. This property causes slowing of conduction in the atrium and ventricle. It may contribute to the antiarrhythmic effect of these agents (though this has been a subject of dispute in the past) (7, 8).

Intrinsic Sympathomimetic Activity. Pindolol and acebutolol are the only available agents with intrinsic sympathomimetic (partial agonist) activity. In addition to preventing access of natural catecholamines to the receptor site, these drugs cause some activation of the beta receptor (9). The major clinical advantage of this property is the possibility for use in patients with resting bradycardia.

The purported advantage of intrinsic sympathomimetic activity (ISA) is as follows: Since the chronotropic effect of these drugs is weak relative to endogenous catecholamines, the net effect in resting subjects is either no change in heart rate or a smaller decrease than that caused by beta blockers lacking ISA. During exercise, when the level of sympathetic tone is high, ISA would add little sympathomimetic effect and the beta-blocking effect predominates. This in turn blocks the expected exercise-induced increase in heart rate and blood pressure response just as occurs with agents lacking ISA (10). Therefore, the drugs with ISA should be valuable in the treatment of angina pectoris without causing unacceptable bradycardia at rest.

On the other hand, these advantages have been questioned. For one thing, most patients taking beta blockers with significant ISA (such as pindolol) do in fact have higher resting heart rates. They also have high rates during sleep, and the use of the agents has been questioned on these grounds. Furthermore, angina pectoris may occur during times when sympathetic stimulation is less than maximal. Thus, the additional sympathetic stimulation induced by drugs with ISA could lessen the overall degree of beta blockade at certain crucial times.

Alpha-Adrenergic Blocking Activity. One drug (labetalol) is available with both beta- and alpha- (i.e., selective alpha-1) antagonist properties. It is 4 to 16 times less potent at alpha than at beta adrenoreceptors. (This varies somewhat over time; early in its use, labetalol's alpha-blocking properties are more prominent than later when some degree of tolerance to these properties develops.) Because of its alpha-blocking actions and in contrast to other beta blockers, labetalol directly reduces rather than increases peripheral vascular resistance. Thus, cardiac output is less affected by labetalol. In addition, in hypertension, labetalol is immediately effective, whereas strict beta blockers have a several-day lag time in treatment of this condition.

Lipid Solubility. The degree of lipid solubility determines both the degree to which the drug crosses the blood-brain barrier and the route and time of elimination of the drug. More lipid-soluble drugs cross the blood-brain barrier to a greater degree (as they do other membranes). This property may be important in the desired effects (antianxiety) but may also contribute to the side effects (fatigue, depression, loss of libido) of these agents. If a patient experiences depression or extreme fatigue while on a lipid-soluble blocker, these symptoms may diminish if the patient is switched to a more water-soluble drug (though the latter are not devoid of central nervous system effects).

Regarding drug elimination, the more lipid-soluble beta blockers are eliminated by the liver and have shorter half-lives. The more water-soluble drugs are eliminated by the kidney and have longer half-lives.

Indications

Angina Pectoris. In the absence of contraindications (for example, asthma) beta blockers are the drug of choice for exertional angina pectoris. Beta blockers reduce myocardial oxygen demand by diminishing or preventing beta-adrenergic stimulation (1). The chronotropic and inotropic responses to stress and exercise are decreased.

Hypertension. Beta blockers, along with thiazide diuretics are now considered first-line drugs in the treatment of hypertension (6). Their mechanism of action is still not entirely clear but appears to be inhibition of renin.

Arrhythmias. By slow conduction through the A-V node, beta blockers are useful in decreasing the ventricular response in atrial fibrillation and in preventing chronic atrial tachycardia. They are used alone or in combination with digoxin. Although beta blockers are useful in acute supraventricular tachycardia, verapamil is now the agent of choice for acute treatment of this arrhythmia. Beta blockers are only occasionally used in treatment of ventricular arrhythmias (with the exception of acebutolol, which seems more effective for these conditions than other beta blockers). The agents are also used for arrhythmias in patients with mitral valve prolapse.

Prevention of Death and Reinfarction in Patients with Myocardial Infarction. Several studies have now shown that beta blockers may diminish both the death rate (in particular the sudden death rate) and the incidence of reinfarction when given to patients after myocardial infarction (11, 12). The protective effect has been found regardless of age, sex, or site of infarction.

Hyperthyroidism. Beta blockers are the drugs of choice to control the heart rate, blood pressure, and other symptoms of sympathetic overactivity in hyperthyroid patients.

Migraine. The mechanism of action of the antimigraine effect of beta blockers' has not been established, but the drugs are clearly useful.

Obstructive Hypertrophic Cardiomyopathy. Beta blockers are used in managing chest pain, palpitations, and syncope, probably by reduction of the outflow pressure gradient (which is exacerbated by beta-receptor stimulation) (13).

Congestive Cardiomyopathy. In spite of their negative inotropic effects, beta blockers have been suggested for use in congestive cardiomyopathy.

A reduction in beta receptors has been associated with refractoriness to endogenous and exogenous catecholamines in patients with heart failure. This is believed to be due to prolonged exposure of these receptors to high levels of catecholamines (14); one of the body's natural response to beta blockade is an increase in catecholamines. Beta blockers also diminish the ability of catecholamines to desensitize receptors. This fact may explain their suggested usefulness in patients with chronic congestive heart failure. An additional effect may be a reversal of catecholamine-induced ventricular arrhythmias and sudden death.

Adverse Effects

The major adverse effects of therapy with beta blockers are related to the predicted effects of beta blockade.

Congestive Heart Failure. Sudden cardiac decompensation is uncommon, but heart failure may develop slowly, in patients with underlying ventricular dysfunction. (Patients with normal ventricular function have little or no reduction of resting cardiac output with beta blockers though exercise output may diminish.)

A-V Block. Beta blockers may cause A-V dissociation and cardiac arrest in patients with preexisting partial heart block owing to underlying conduction system disease or to other medications that also affect the tissues (digoxin, calcium channel blockers). Labetalol appears to affect A-V conduction less (15).

Rebound and Tolerance. A withdrawal syndrome after cessation of chronic beta-blocker therapy has been well described. The possible cause is an increase in receptor number. It is believed that the number of adrenoreceptors (alpha and beta) is subject to wide variations, and that changes in tissue concentrations of receptors are responsible for fluctuation in sensitivities to drugs (7).

The number of beta-adrenergic tissue receptors is apparently inversely related to the degree of stimulation by catecholamine agonists. When sympathetic nervous system activity is high, the number of beta-adrenergic receptors decreases (down-regulation); when activity is low, the number of receptors increases (up-regulation) (16). Up- and down-regulation occur rather quickly.

Chronic exposure to beta blockers results in an increase in the number of beta receptors and thereby supersensitivity to beta agonists on withdrawal (17). This may explain the withdrawal phenomenon seen at times on sudden discontinuation of beta blockers in patients with ischemic heart disease. In these patients an abnormally increased number of beta receptors are suddenly open to endogenous catecholamine stimulation, which in turn may precipitate angina or myocardial infarction (18). It should be noted that clinically apparent withdrawal syndromes are not that common and seem less likely with some of the beta blockers. The syndrome is prevented by tapering rather than abruptly withdrawing the blockers. In the case of propranolol one may give a modified dose on the third day after withdrawal (the time of peak rebound effect).

Bronchospasm. As mentioned above, blockade of beta-2 receptors may induce bronchospasm in susceptible patients. This possibility is diminished by the use of cardioselective agents but may still occur with these drugs at higher dose ranges.

Hypoglycemic Response. Beta blockers augment the hypoglycemic action of insulin by decreasing the compensatory effect of sympathoadrenal activation. In addition, the associated tachycardia and other responses to hypoglycemia may be blunted, preventing the patient from recognizing the need for glucose intake.

Other Adverse Effects. Other adverse effects include depression and fatigue, which may be less with the more water-soluble agents; arthralgias and arthritis, nausea, vomiting, diarrhea, rash, impotence, thrombocytopenia, and muscle cramps have also been reported.

Available Agents

The characteristics of the eight drugs discussed below are summarized in the Table.

Atenolol. Atenolol is approved for hypertension. Initial dosage is 50 mg daily, which may be increased to 100 mg daily. Further increases in dosage are unlikely to produce any further benefit. Atenolol is excreted by the kidneys; therefore, the dose must be adjusted for poor renal function.

Atenolol is one of the three available cardioselective drugs. It has a long $t_{1/2}$, allowing once-daily administration.

Nadolol. Nadolol is currently approved for angina and hypertension. Dosage varies from 40 mg to 240 mg daily. Nadolol is not cardioselective. Its long $t_{1/2}$ also allows once-daily administration. Nadolol is excreted by the kidneys.

Pindolol. Currently, pindolol is approved for hypertension. It has significant ISA. The dose ranges from 20 mg to 60 mg daily given in twice-a-day dosage. Pindolol is partially metabolized by the liver and partially excreted in the urine.

Timolol. Timolol is approved for hypertension and prevention of sudden death after myocardial infarction. It was the first drug to be approved for the prevention of sudden death and recurrent infarction following myocardial infarction (12). The recommended dose is 10 mg twice daily. When the drug is used for hypertension, doses up to 60 mg daily are recommended.

Propranolol. Propranolol was the first beta blocker to be approved and is still the most widely used. It is at present approved for the treatment of angina pectoris, hypertension, hypertrophic cardiomyopathy, post-myocardial-infarction prophylaxis, migraine prophylaxis, and management of certain arrhythmias.

Propranolol has the highest lipid solubility of the beta blockers, making it most useful when central nervous system effects are desired (e.g., in anxiety or prevention of tremor). The clinical importance of the membrane-stabilizing activity is not known. Propranolol is metabolized in the liver and undergoes extensive first-pass metabolism. An intravenous preparation is also approved. Recently, a long-acting (that is, retarded-absorption) form of propranolol has been developed that can be given once or twice a day.

Metoprolol. Metoprolol was the first cardioselective beta blocker available in the United States. The starting dose is 50 mg twice daily. At or above a dose of 200 mg/day the cardioselective effect is not prominent. Metoprolol is also available for intravenous use.

Labetalol. Labetalol is a competitive antagonist at both alpha and beta receptors. It has been used for the treatment of hypertension and angina pectoris (19). (It has also been shown to cause some of its vasodilator action by direct activation of beta-2 adrenoreceptor [20].) On initi-

TABLE
Available Beta-Adrenergic Blocking Agents

	Relative beta-1 selectivity	Alpha blockade	Intrinsic sympathetic activity	Membrane-stabilizing activity	Lipid solubility	Half-life (hr)†	Predominant route of elimination
Acebutolol (Sectral)	+	0	+	+	+	3–4	Renal
Atenolol (Tenormin)	+ +	0	0	0	–	6–9	Renal
Labetalol (Normodyne)	0	+	0*	0	+	3–4	Hepatic
Metoprolol (Lopressor)	+ +	0	0	0	+ +	3–4	Hepatic
Nadolol (Corgard)	0	0	0	0		14–24	Renal
Pindolol (Visken)	0	0	+ +	+	±	3–4	Renal and hepatic
Propranolol (Inderal)	0	0	0	+ +	+ +	3–4‡	Hepatic
Timolol (Blockadren)	0	0	0	0	+	4–5	Renal and hepatic

* Labetalol has beta-2 agonist properties.
† Effect of beta blocker is more sustained than its plasma half-life.
‡ A long-acting (retarded-absorption) form of propranolol is available.

ation of treatment with labetalol, alpha-blocking properties are very prominent; however, tolerance develops to this effect, and with chronic therapy the effects of beta blockade predominate.

Alpha-blocking effects of labetalol lead to a reduction in pulmonary and peripheral vascular resistance. As a consequence of afterload reduction, it causes less decline in ventricular function than drugs with strictly beta-blocking properties (20). Labetalol is approved for use in hypertension. It is particularly useful in acute hypertension (such as during general anesthesia [21]) where, unlike other beta blockers, it lowers blood pressure immediately. It does this by virtue of its alpha-blocking properties.

Acebutolol. Acebutolol is the most recent beta blocker approved for clinical use in the United States (22). It is a cardioselective beta blocker with mild intrinsic sympathomimetic and membrane-stabilizing activities. It is approved for use in hypertension and ventricular arrhythmia.

Summary

With the availability of a wide range of beta-blocking drugs with differing characteristics, the use of these agents will continue to broaden. By understanding the clinical distinctions among these drugs, it is possible to tailor therapy to the individual patient and thus achieve greater overall therapeutic precision.

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The Role of Some Noncardiac Factors in Determining Hemodynamic Alterations during Cardiac Surgery

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During the last two decades, attention has been paid to myocardial performance as the main determinant of hemodynamic changes during cardiac surgery. However, the role of noncardiac factors, such as changes in peripheral circulation and neurogenic control of circulation, has been overlooked. This article focuses on some of the noncardiac factors that play an important role in hemodynamic changes during cardiac surgery.

Patterns of Hemodynamic Alterations during Cardiac Surgery

Studies of 24 patients (1) with good to moderately impaired ventricular function, undergoing myocardial revascularization surgery and receiving the same anesthetic agents and hemodilution during cardiopulmonary bypass, revealed the following distinct hemodynamic patterns (Fig. 1):

Five minutes after induction and intubation, hemodynamic status remained remarkably stable, although laryngoscopy and endotracheal intubation are strong sympathetic stimulants and can increase heart rate and mean arterial pressure.

After sternotomy and pericardectomy, both systolic blood pressure and cardiac index fell, and the systemic vascular resistance increased slightly. Intermittent positive pressure ventilation and opening of the chest may have contributed to such hemodynamic changes.

Variations during cardiopulmonary bypass were not addressed in this study partly because cardiac output is mechanically controlled and there are many other variables.

Immediately after cardiopulmonary bypass, the hemodynamic changes followed a remarkably uniform pattern. This consisted of decreased systemic vascular resistance and increased cardiac output, as the right and left ventricular filling pressures were maintained close to control values by transfusion. The drop in systemic vascular resistance was ascribed to hemodilution with its consequent significant reduction in hematocrit value. In 1961, Guyton and Richardson (2) reported that venous return is inversely related to hematocrit levels. Other hemodynamic studies, both experimental and clinical, have confirmed that cardiac output will increase markedly in patients with good ventricular function in response to reduction in the circulating red cell mass (3–5).

In the study I conducted with colleagues (1), the patients did not become hypotensive; the increased output compensated fully for the reduced systemic vascular resistance. The results might have been different in the presence of significant left ventricular impairment. The diseased myocardium imposes strict limits on the volume of blood that can be ejected by the heart, despite the needs and status of the peripheral circulation (6). The weakened heart may not have the same response to the increased preload. In this situation, hypotension may be inevitable, with further reduction in myocardial oxygen supply and deterioration of myocardial performance.

Late in surgery and early postoperatively: At the end of the operation, from the time of sternal closure and for the first hour postoperatively, an unexpected hemodynamic pattern developed. The systemic vascular resistance began to rise and continued to do so, despite the presence of he-

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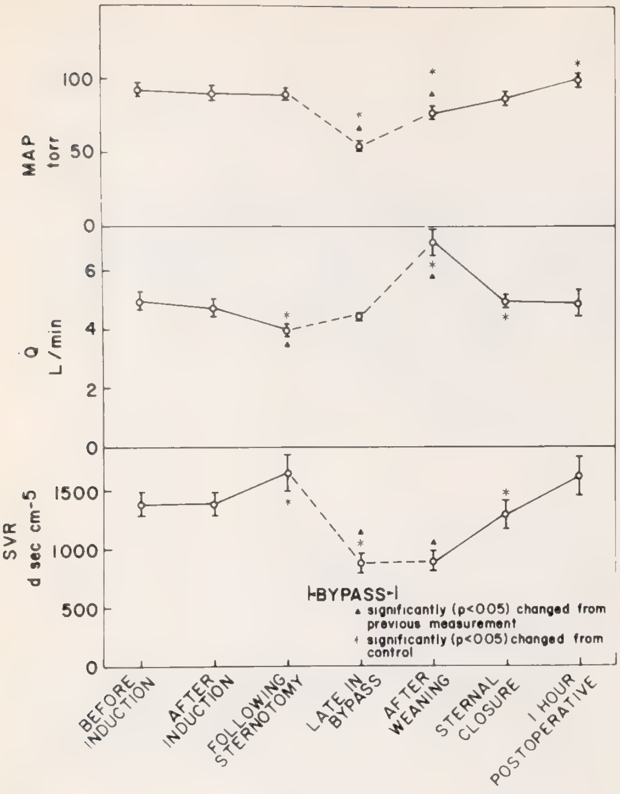


Fig. 1. Evolution of hemodynamic parameters during coronary surgery. MAP, mean arterial pressure; SVR, systemic vascular resistance; $\dot{Q}$, cardiac output.

modilution. Concomitantly, the elevated cardiac output began to decrease, returning to control values. The mean arterial pressure rose significantly to higher levels than immediately after bypass and reached levels higher than those measured in the initial control period.

This hemodynamic pattern of increasing systemic vascular resistance and blood pressure with practically unchanged levels of cardiac output, in the presence of unchanged pulmonary capillary wedge and central venous pressures, has some resemblance to the hemodynamic pattern of post-myocardial revascularization hypertension described by Fouad, Estafanous, and Tarazi (7).

Throughout all stages of this study, the hematocrit level correlated significantly with cardiac output, as previously reported by others (2, 3). However, arterial pressures did not correlate with the changes in cardiac index (Fig. 2). Arterial pressure variations correlated strongly with systemic vascular resistance (Fig. 3), signifying that pressure was mainly dependent on changes in vascular resistance (8, 9). Although systemic vascular resistance is a calculated value dependent on some theoretical assumptions, its variations in short-term situations can be considered a clinically valid index of changes in vascular caliber (8).

These conclusions have some important clinical implications: If fluctuations in arterial pressure within the phases of coronary arterial operations are mainly related to peripheral factors (viscosity and vascular caliber), then the treatment of hypotension or hypertension in these conditions must take into account these peripheral factors and not be directed solely by assumed alterations in myocardial performance.

Several conclusions and clinical applications emerged from this study:

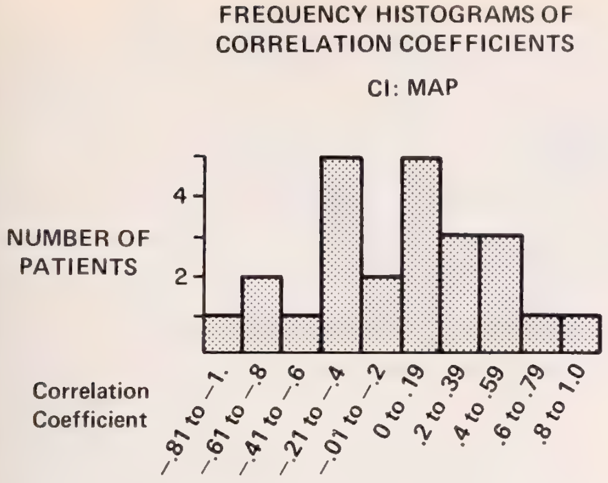
First, in this clinical setting, the changes in systemic vascular resistance were more important than changes in cardiac output in determining mean arterial pressure levels.

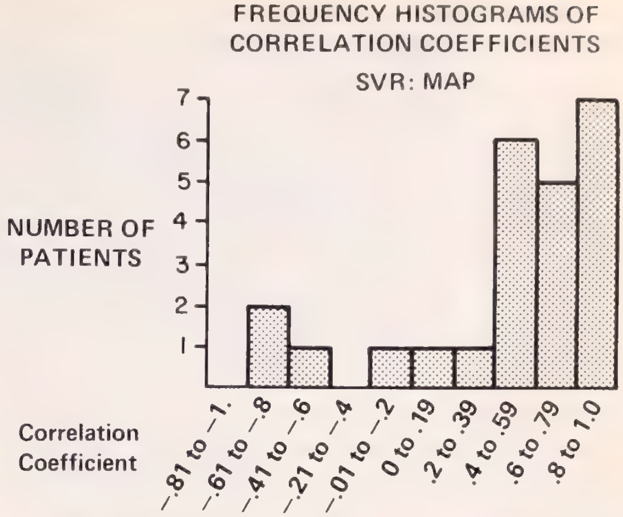
Second, our results apply only to patients with good ventricular function whose cardiac output can be increased in response to hemodilution and decreased systemic vascular resistance. Cardiac output might not increase in patients with impaired ventricular function, and they could therefore be more vulnerable to hypotension when systemic vascular resistance falls. This limitation is of practical importance when hemodilution is utilized.

Third, all hemodynamic variables must be considered in the choice of pharmacologic support of the circulation during cardiac operations.

Hemodilution and Response to Vasoactive Drug Therapy

Hemodilution is currently an accepted practice during surgery. The effect of hemodilution on systemic vascular resistance changes has just been emphasized. In a clinical setting, the question arises whether hemodilution has any effect on vasoactive drug therapy, because little, if any, attention has been paid to its effects on the vascular reactivity to alpha-adrenergic stimulation. With colleagues, I investigated the influence of hemodilution on vasoconstrictor responses to catecholamines in isolated-hindlimb rat preparations (10) (Fig. 4a). We then compared the response to norepinephrine (nonselective alpha-1 and alpha-2) with the response to phenylephrine (selective alpha-1). Our studies demonstrated the following: During hemodilution, there was blunting of the vasopressor response to norepinephrine at all doses. That blunting was partially reversed by two maneuvers: (a) reversing hemodilution (Fig. 4b), and (b) increasing the blood flow to maintain





Figs. 2,3. Frequency histograms of correlation coefficients. **Fig. 2. Left** cardiac index (CI): mean arterial pressure (MAP). **Fig. 3. Right** systemic vascular resistance (SVR): mean arterial pressure (MAP).

the initial perfusion pressure. Normalization of the hematocrit and increase in blood flow presumably improved delivery of oxygen to tissues. In a similar rat hindlimb preparation, the vasopressor response to phenylephrine was not changed.

The difference in sensitivity between alpha-1- and alpha-2-mediated vasoconstriction during isovolemic hemodilution was significant. One possibility—a tentative explanation—is that the processes utilized by the two adrenergic excitation-contraction pathways differ in their dependence on oxygen supply. Practically, whatever the explanation is, this suggests that use of a selective alpha-1 agonist may be more useful than norepinephrine in controlling hypotensive episodes during hemodilution.

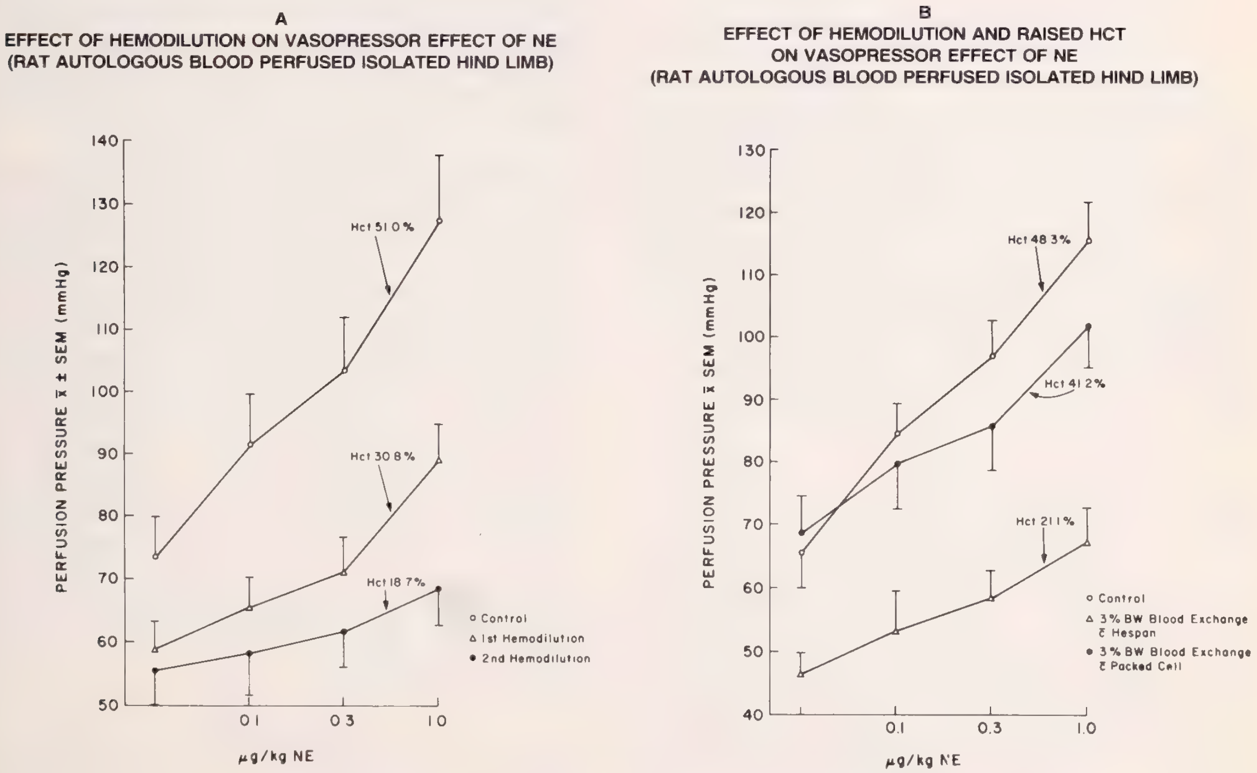


Fig. 4a,b. Influence of hemodilution on vasopressor response; NE, norepinephrine; Hct, Hematocrit; BW, body weight.

Calcium Channel Blockers and Response to Vasoactive Drug Therapy

Most calcium channel blockers are peripheral vasodilators, mainly arteriole dilators (11). Clinically, we observed that some patients, particularly the elderly and those receiving large doses of calcium channel blockers, are more vulnerable to hypotension during cardiac surgery. Such a drop in blood pressure was accompanied most of the time by decreased systemic vascular resistance and adequate, even high, cardiac output. We also observed that hypotension related to calcium channel blocker therapy is resistant to treatment and usually requires larger doses of vasopressors. Pedrinelli and Tarazi (12) demonstrated in experimental studies that the drop in systemic vascular resistance secondary to calcium channel blockers is more responsive to selective alpha-1 pressors and much less responsive to alpha-2 pressors.

From all the above findings, it is clear that hypotension in the presence of hemodilution and/or calcium channel blocker therapy can be resistant to treatment by selective alpha-2 pressors and more responsive to selective alpha-1 pressors. However, in the presence of impaired ventricular function, an inotropic agent may be required as well as the selective alpha-1 pressor.

Neurogenic Control of the Circulation

The role of neurogenic control of the circulation in determining hemodynamic changes during cardiac surgery has been overlooked. After our first description of postmyocardial revascularization hypertension, we postulated that the rise in the systemic vascular resistance and blood pressure is of neurogenic origin. This was later confirmed, since interruption of the afferent sympathetic pathways by stellate ganglion blockade normalized the blood pressure for those who developed postmyocardial revascularization hypertension (13).

Such findings attracted our attention to the role of neurogenic factors in hemodynamic changes during cardiac surgery. Since then, the role of the cardiovascular sympathetic afferent fibers and their locations in the cardiovascular system have been comprehensively reviewed by Malliani (14). These cardiovascular afferent fibers originate from several locations, such as the atria, ventricles, coronary vessels, and aorta. Mechanical and chemical stimulation of such receptors can cause significant changes in the arterial blood pressure levels (14). Stimulation of these receptors explains the changes in blood pressure during cannulation of the big vessels (Fig. 5). Such stimulation may also explain the changes in the blood pressure in response to manipulation of the heart during cardiopulmonary bypass when it is completely excluded from the circulation. Chemical stimulation of such receptors, as produced by myocardial ischemia, causes the rises in blood pressure noticed during the early stages of myocardial ischemia (15). Not infrequently, the rise in blood pressure is one of the early signs of myocardial ischemia and precedes rhythm changes, such as ventricular tachycardia. Also, the rise in blood pressure following resuscitation of a cardiac arrest was explained on the basis of chemical stimulation. However, in the clinical setup of cardiac surgery, including anesthesia, cardiopulmonary bypass, and surgical interference, how many of these afferent reflexes are stimulated or blunted is still unclear.

Anesthesia and Baroreceptor Function

Various anesthetic agents depress the baroreceptor function. Such an effect is dependent on the type of anesthetic used and its concentration. Halothane decreases the baroreceptor response of both sympathetic and parasympathetic systems. Isoflurane has the same effect to a lesser degree. Kotrly et al (16) recently demonstrated that morphine also blocks both vasopressor and vasodepressor reflexes. However, there is no clear information about the effects of the potent opioids (fentanyl and sufentanil) on baroreceptor function.

Narcotics and Systemic Vascular Resistance

My group is currently studying the effects of various narcotics and their method of administration on the changes in perfusion pressure in hindlimb preparations of rats. This preparation allows us to study the effects of drugs on the peripheral circulation while excluding the heart as a factor (17). The initial results demonstrate that more potent narcotics such as fentanyl and sufentanil produce less vasoconstriction or rise in the systemic vascular resistance than morphine does. It also seems that continuous infusion of such narcotics minimizes the vasopressor effect of narcotics. These are only preliminary observations which point to the need to investigate such findings more elaborately.

Summary

All of our experience leads us to believe that the challenge of the future is to fully understand

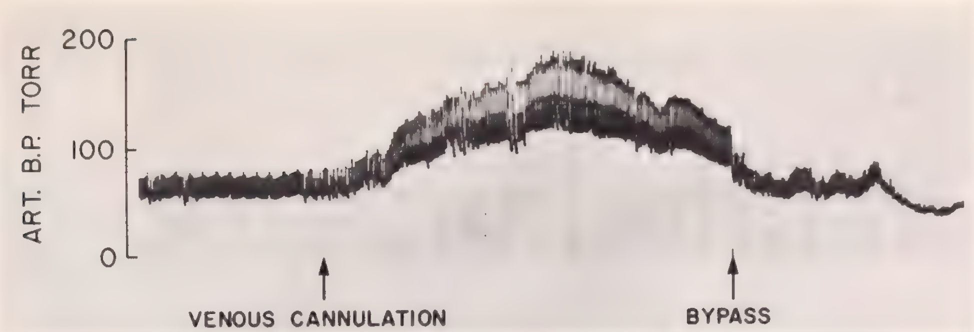


Fig. 5. Rise in arterial blood pressure (ART. B.P.) in response to venous cannulation.

the hemodynamic alterations that occur during cardiac surgery and to appreciate the roles of neurogenic control of the circulation and other noncardiac factors in hemodynamic changes.

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General Articles, Specialty Notes, and Students' Corner

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Multiple Synchronous Scar-Related Lung Carcinomas: Report of a Case and Review of the Literature

STEWART H. GLEISCHMAN, M.D.

Abstract

An unusual case of multiple synchronous scar-related lung carcinomas is described. Scar-related lung tumors and multiple lung carcinomas are two variants of lung pathology with separate diagnostic criteria. This case satisfies the recognized criteria for the diagnosis of both entities. The incidence of scar-related lung tumors has been noted to be increasing. The clinical significance of this entity, however, remains controversial. The diagnosis of multiple primary lung tumors has a grave prognosis. In order to avoid errors in diagnosis or delays in therapy, a second lung tumor must be considered when the diagnosis of recurrent or metastatic lung carcinoma is made.

Case Report

An asymptomatic 73-year-old white woman was discovered to have a 2.5-cm right-upper-lobe lesion on a routine chest radiograph. Tomograms confirmed the lesion and revealed some lobulations but no calcifications, cavitation, or hilar adenopathy. Medical history included essential hypertension, hypothyroidism of 30 years' duration, and lumbar osteoarthritis. The patient had a 70 pack/year smoking history. Her father died of an unknown cancer at age 44, and her sister died of lung cancer.

During hospitalization, examination of the sputum for malignant cells was negative on three occasions. Flexible bronchoscopy revealed no mucosal abnormality. Bronchial washings and biopsies were negative for malignancy. Liver-spleen and bone scans were also negative. Through a right thoracotomy, a wedge resection was submitted for frozen-section analysis. After this, a right upper lobectomy was performed.

Pathology

The resected wedge measured 5 cm and contained a 0.8-cm firm, discrete gray tumor nodule with a stellate border (tumor A). The right upper lobe revealed a second 0.6-cm firm gray mass (tumor B) deep to the site of the wedge resection. A third mass (tumor C), measuring 1.7 cm, was found in the apical segment. None of the tumors involved the pleural surface. The remainder of the lobe exhibited multiple foci of parenchymal fibrosis and fibrotic pleural plaques.

Microscopic examination of each of the tumors revealed a centrally located dense scar containing nests of tumor cells with neoplasm extending into adjacent lung. Tumor A was composed of cells with large vesicular nuclei and abundant cytoplasm (Fig. 1). No definite evidence of squamous or glandular differentiation was found, and the tumor was classified as a large-cell undifferentiated carcinoma. Tumor B exhibited stratification, keratinization, and intracellular bridges, findings characteristic of squamous cell carcinoma (Fig. 2). Tumor C, a bronchioloalveolar carcinoma, was characterized by cuboidal, columnar, or peg-shaped cells lining alveolar walls (Fig. 3). Pulmonary tissue away from the three neoplasms showed multiple foci of interstitial fibrosis. Small

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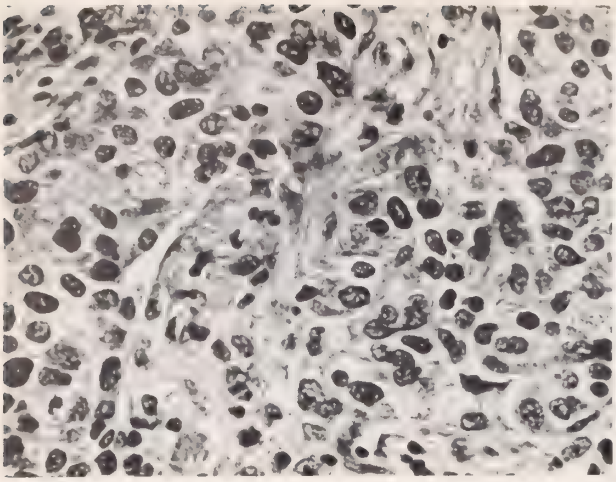

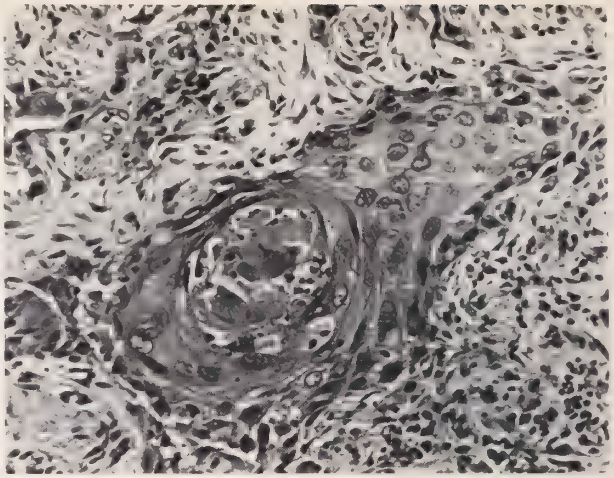

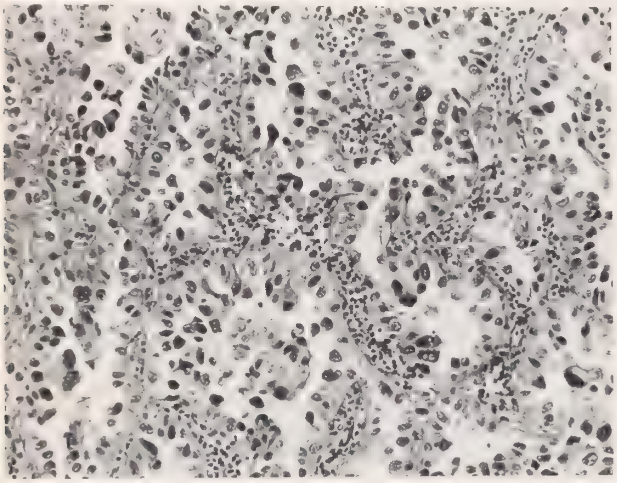

Fig. 1. Tumor A, showing large cells without evidence of glandular or squamous differentiation. Tumor was classified as large-cell undifferentiated carcinoma (H & E × 100).

Fig. 2. Tumor B, showing nest of tumor cells with stratification and keratinization characteristic of squamous cell carcinoma (H & E × 150).

Fig. 3. Tumor C, bronchioloalveolar carcinoma. Tumor cells line alveolar walls and project into alveolar spaces (H & E × 40).

bronchioles and alveoli in some of the fibrotic areas respectively exhibited squamous metaplasia and alveolar cell hyperplasia with varying degrees of atypia. Lymph nodes were not involved.

Discussion

This is an unusual case of multiple scar carcinomas of the lung. The original description of scar carcinoma of the lung is credited to Friedrich in 1939 (1). Since then, a number of series have been published. Between 10% and 45% of all lung carcinomas are scar-related (2–4). This figure rises to between 45% and 75% when only peripheral cancers are considered (2, 3). It has been further observed that 75% of these lesions are located in the upper lobes, right slightly more frequent than left (2). The wide range in reported incidence of this entity is due in part to different definitions of what constitutes a scar-related lung cancer. According to Friedrich (1), scar-related lung tumors are peripherally located tumors with no evidence of bronchial origin, occurring around true hyalinized scar and often associated with pleural puckering and anthracotic pigment.

In a large review extending over a 21-year period, Auerbach et al (2) demonstrated that the proportion of scar-related lung cancers increased from 2% in 1955–1960 to 16% in the 1970–1975 period. One explanation for the trend is the increased age of the population. The cause of scarring appears unimportant and includes thromboembolic phenomena, pneumoconioses, infection, and foreign-body reaction (2, 5). No correlation has been demonstrated with cigarette usage.

Carcinomatous change in previously damaged tissues is a well-accepted feature of several organ systems, although the cause is not known. Raeburn and Spencer (5) proposed that blockage of lymphatic channels by scar formation might account for the development of cancer by increasing the concentration of carcinogens. This concept is supported by the observation of increased amounts of anthracotic pigment, cholesterol, and the breakdown products of elastic tissue in the area surrounding scar-related lung tumors (5).

Ripstein and Spain et al (6) made several hypothetical points concerning the origin of scar-related tumors. First, carcinogenesis and the scarring process may have a common etiologic background. Second, tumors may result from a nonspecific reactive hyperplasia. And third, fibrosis and the associated hyperplasia may make the epithelium more susceptible to carcinogenic influences. Collagen studies performed on tumor-related pulmonary scars revealed an active fibrotic response. This may support host response as a factor in the scarring process associated with pulmonary neoplasia (7). The case presented supports the concept that areas of pulmonary scarring may be fertile environments for neoplastic transformation.

Multiple primary carcinoma of the lung is another variant of lung pathology. These tumors can be either synchronous (simultaneous) or metachronous (consecutive) and can be of similar or dissimilar histologies; again, the exact incidence is uncertain, partly because of disagreement over the definition. Billroth and Winiwarter (8) in 1887 proposed that a second primary neoplasm exists if the tumors (a) are separate in location, (b) differ in histology, and (c) produce their own metastasis. These criteria were revised, and at present most authors accept the diagnosis of separate primary lung cancers if they (a) are anatomically discrete, (b) differ in histology, and (c) arise from separate bronchial mucosa (4, 9).

In an autopsy series by Auerbach et al (10), the incidence of multiple primary lung cancers ranged from 3.5% to 14.5% depending on whether "strict" or "less strict" criteria were used. Rohwedder and Weatherbee (4) demonstrated an incidence of 0.2%–1.8% in their review of the literature in 1974. Razzuck et al (9) reported the occurrence of a second primary lung cancer in 3.1% of patients surviving 5 years, indicating a need for long-term follow-up. Bennett et al (3) suggested that the incidence is difficult to ascertain accurately since the second primary tumor may be misinterpreted as metastasis or recurrence, although a bronchiogenic neoplasm appearing more than 30 months after resection is unlikely to be metastatic, according to LeGal and Bauer (11).

The case reported here satisfies the recognized criteria for scar-related carcinoma and multiple primary lung cancers. Each tumor was discrete, each occurred in hyalinized fibrous tissue with heavy concentrations of anthracotic material, and there were three different histologic cell types. To date, scar-related lung carcinomas representing all the recognized histologic varieties have been reported. Adenocarcinoma (bronchioloalveolar) appears to be the most common cell type (2). Multiple scar-related carcinomas appear to be uncommon. In data updated but including that presented by Yokoo and Suckow (12), 184 cases of scar-related lung carcinomas are identified with only two cases of multiple tumors, neither with differing histologies. In the review of Rohwedder and Weatherbee (4), 72 cases of multiple primary lung carcinomas with dissimilar histologies were identified. Razzuck et al (9) contributed four more cases in their review of 34 dual primary lung tumors. No mention is made of the presence of surrounding scar tissue and no case of more than two histologies is reported by either author.

Huckill and Stern (13) and Bennett et al (3) reported unimproved survival when lung tumors are scar-related. This has been disputed by Freant et al (14), who challenged the notion that scar-related lung carcinoma is a separate clinical entity. In recent data reported by Shimosato et al, a poorer prognosis was found in small peripheral adenocarcinomas associated with increased collagenization in the fibrotic focus (15). The prognosis in multiple primary lung tumors is noted to be grave (9). Accurate survival statistics are difficult to achieve because no large series is available and because of the influences of selection, since a patient must survive long enough to develop a second carcinoma. In their report of the Memorial Hospital experience, Martini and Melamed (16) noted 54% five-year survival with the first tumor and 28% and 11% five-year survivals for synchronous and metachronous tumors, respectively. Surgical treatment remains the primary therapeutic modality, although the extent of resection is governed by the patient's physiologic reserve.

Addendum

This patient is now 12 months postlobectomy and recently returned to Cedars-Sinai Medical Center for a supraclavicular node biopsy. This specimen revealed metastatic large-cell undifferentiated carcinoma.

Acknowledgments

I express appreciation to Dr. E. Kompaniez for bringing this case to my attention, Dr. L. Morgenstern for editorial assistance, and Dr. G. Nash for his help in preparing the pathologic material.

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Surgical Pathology Notes

Ira S. Schwartz, M.D., Editor

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Malignant Fibrous Histiocytoma of the Maxillary Sinus

Pamela D. Unger, M.D., Mamoru Kaneko, M.D., and Swan N. Thung, M.D.

Malignant fibrous histiocytoma (MFH) is one of the most common soft-tissue sarcomas in adults (1, 2). The extremities and retroperitoneum are the usual locations. These tumors have also been reported to arise in bone; however, the maxillary sinus is an unusual site (3). Nineteen previous cases of MFH of the maxillary sinus are described in the literature. In all these cases, a portion of the tumor displayed the diagnostic microscopic features. Although it is infrequent in this locale, MFH should be included in the differential diagnosis when the pathologist is confronted with a spindle-cell tumor.

We recently studied such a case in a man with nasal obstruction. The lesion exhibited the characteristic fibroblastic cells arranged in a cartwheel pattern, abundant histiocytes, and atypical multinucleated giant cells. Immunohistochemistry was positive for alpha$_1$-antitrypsin and S-100 protein. Ultrastructural studies were nonspecific but consistent with a mesenchymal neoplasm.

Case Report

The patient, a 45-year-old Hispanic man, came to The Mount Sinai Hospital with a history of right-sided nasal obstruction for several months. The physical examination was noteworthy for right-sided proptosis and a nasal mass on the right side. Admission laboratory values were normal. A paranasal sinus CT scan revealed a right antral mass that destroyed the entire medial and posterior lateral wall, invaded the intratemporal fossa and pterygoid muscles, and extended cranially to erode a portion of the greater wing of the sphenoid and orbital floor. The patient underwent a biopsy followed approximately 1 week later by a right maxillectomy. At surgery, the entire tumor was believed to be excised. A second paranasal CT scan three months after the operation suggested a recurrent tumor in the area.

Pathology. The right maxillectomy specimen measured approximately 8 cm in greatest length (Fig. 1). A bulging, nodular mass, measuring 5.5 × 5.0 × 5.0 cm, obliterated the maxillary sinus cavity. Externally, the mass was encased by a thin pink fibromembranous tissue. The cut surface revealed rubbery, firm, tan, vaguely trabeculated tissue with focal areas of hemorrhage and necrosis. The lesion abutted laterally against the adjacent maxillary bone but did not invade into it. The medial margin was covered by a pink mucosa that was focally ulcerated and involved with tumor.

Microscopic Examination. The initial biopsy and the main specimen had similar histology. The tumor was cellular and characterized by numerous bizarre, multinucleated giant cells and haphazardly arranged spindle cells with an occasional storiform pattern (Figs. 2, 3). A small number of foamy histiocytes were observed. The lesion focally exhibited a myxoid stroma or, rarely, hemangiopericytomalike features. Mitoses were frequent and averaged one per high-power field. The tumor extended to the posterior, lateral, and superior surgical resection margins.

Immunohistochemical studies performed on the lesion included lysozyme, alpha$_1$-antitrypsin, keratin, and S-100 protein. Spindle tumor cells were positive for alpha$_1$-antitrypsin, keratin, and S-100 protein by the avidin-biotin peroxidase complex method and plump histiocytes for alpha$_1$-antitrypsin only (Fig. 4).

Electron microscopy was performed on a fragment of the tumor after fixation in 3% glutaral-

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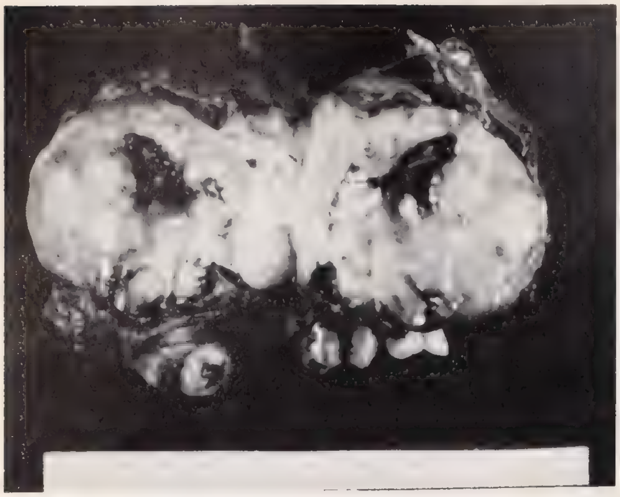


Fig. 1. Gross appearance of maxillectomy specimen. Bisected nodular mass obliterates maxillary sinus cavity. Cut surface reveals rubbery, tan, vaguely trabeculated tissue with focal areas of hemorrhage and necrosis.

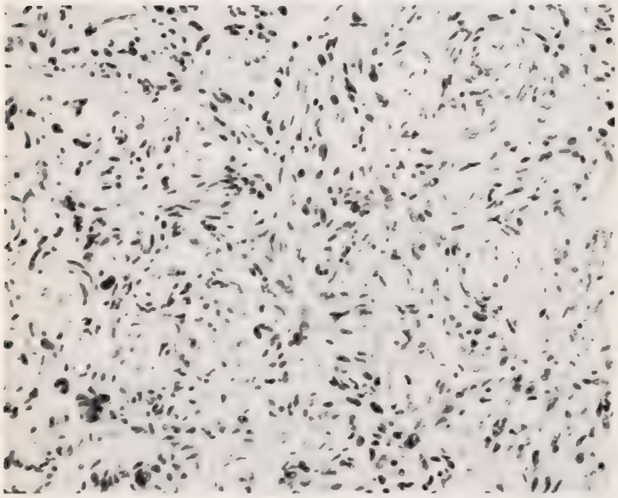
dehyde. Loosely arranged spindle cells embedded in collagen matrix were present. The cytoplasm contained abundant intermediate filaments, some mitochondria, and a paucity of rough endoplasmic reticulum and Golgi complexes. Pinocytotic vesicles were numerous along the plasma membrane, and there were patches of basal lamina opposite hemidesmosomes. These features are nonspecific and could be attributable to several soft-tissue neoplasms, including fibrous histiocytoma, leiomyosarcoma, or a tumor of nerve sheath origin (4).

Discussion

Malignant fibrous histiocytoma (MFH) is the most common soft-tissue sarcoma occurring in the fifth to seventh decades of life (1). The most frequent sites, in decreasing order, are the lower extremity, upper extremity, and retroperitoneum. Histologically, the diagnosis is established by the presence of fibroblasts in a storiform or cartwheel pattern, pleomorphic areas containing plump histiocytes, and multinucleated giant cells. Mitoses are usually numerous. The percentage of each of these elements is variable, depending on the lesion and which field of an individual tumor is examined. Histologic features such as anaplasia or mitosis have not had consistently predictive value in determining a patient's clinical course.

Enzinger and Weiss have subdivided MFH into the following groups: storiform-pleomorphic, myxoid, giant cell, and inflammatory (1, 2). All variants have at least some areas with the classic storiform-pleomorphic pattern. The latter three subtypes also have prominence of either myxoid stroma, osteoclast-type giant cells, or xanthoma and inflammatory cells, respectively. A fifth subtype, angiomatoid, contains features of a fibrohistiocytic and vascular neoplasm.

Nineteen previous cases of maxillary sinus MFH have been reported in the literature and are summarized in the Table (5–16). The largest series comes from Perzin and Fu (5). Several patients had tumor involvement of neighboring sinuses and soft tissues. The patients' ages ranged from 23 to 80 with an average of 50 years. There



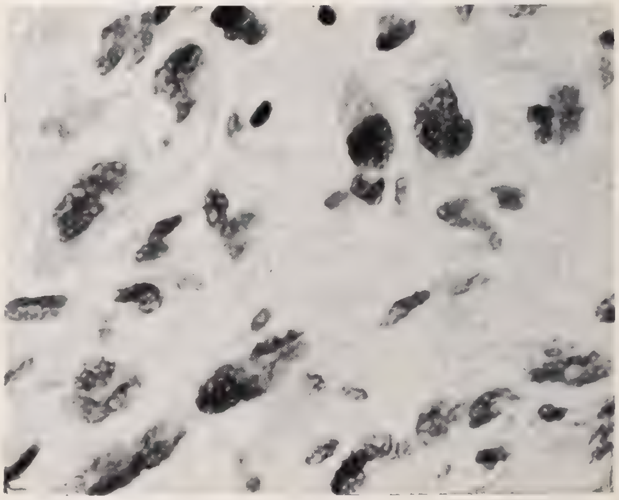


Fig. 2. Left Microscopic section of maxillary mass showing spindle cells in storiform pattern (H&E, ×100).

Fig. 3. Right Microscopic section showing bizarre, multinucleated giant cells, spindle cells, and plump histiocytic cells (H&E, ×400).

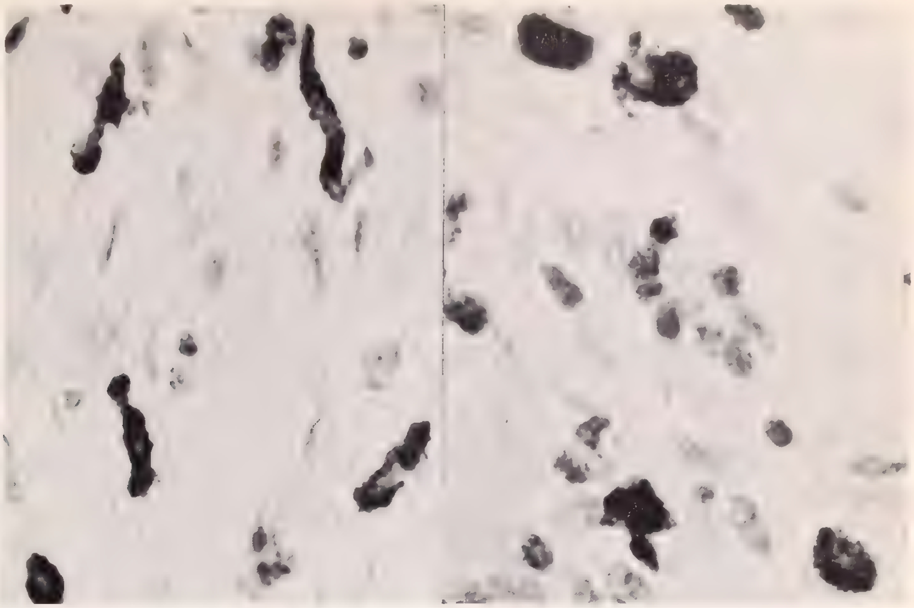


Fig. 4. Left Tumor cells containing S-100 protein in cytoplasm (ABC method, ×400). **Right** Tumor cells with abundant cytoplasm containing alpha-1-antitrypsin (ABC method, ×400).

is a slight female predominance, with a female-to-male ratio of 1.7:1. Most of these patients initially had abnormalities referable to the paranasal sinus region. The most frequent symptoms were a swelling or mass in the maxillary region, facial pain, nasal obstruction, and epistaxis.

These tumors run a spectrum histologically identical to their soft-tissue counterparts, and likewise, the microscopic findings did not consistently correlate with the patient's clinical outcome. Distant metastases appear to be associated with a poor prognosis. Four patients who died within a year of diagnosis had evidence of metastases during the course of their disease (9, 13, 15, 16). No autopsy was performed on the patient reported by Lopez et al; however, clinically, the patient had enlarged cervical lymph nodes (16). In the case of Slootweg and Muller, before death the patient had metastases to the cervical lymph nodes, but at autopsy, no residual tumor was found (9). Each of the remaining two patients had bone marrow involvement. In the case of Merrick et al, there were also liver metastases, and in the case of Sonobe et al, widespread metastases to the lungs, pleura, pancreas, and kidneys were discovered at autopsy (13, 15). As mentioned by other authors, this tumor has a greater propensity for lymph node metastasis than most sarcomas (1, 9).

MFH of the maxillary sinus is an aggressive neoplasm with local invasion and frequent recurrences. Radical surgery is the treatment of choice. Adjunct radiation therapy and chemotherapy have been employed; however, the most efficacious management of these patients has yet to be determined. Although 5-year survival figures are not available for MFH of the maxillary sinus, the rate is approximately 60% for lesions of the entire head and neck region (17, 18).

The histogenesis of MFH is controversial. Initially the origin was believed to be histiocytic and the histiocytes were thought to transform morphologically and functionally into fibroblasts (facultative fibroblasts). Enzinger and Weiss regard these tumors as arising from primitive mesenchymal cells that can differentiate into fibroblasts or histiocytes (1). Perzin and Fu held the same opinion on MFH of the paranasal sinuses (5). Support for this theory has been furnished by ultrastructural studies (19). Three cell types have been identified: fibroblasts with elongated nuclei, prominent nucleoli, and abundant RER, which may contain actinlike filaments; histiocytes with oval or lobated nuclei, cytoplasmic processes, prominent Golgi complexes, numerous lysosomes, and lipid droplets; and a primitive mesenchymal cell that contains few organelles except for free ribosomes in a narrow rim of cytoplasm.

In the case presented, the diagnosis of MFH was established by light microscopy. The characteristic storiform pattern, histiocytes, and multinucleated giant cells were observed. Immunohistochemistry and ultrastructural studies further substantiated the diagnosis. Immunohistochemistry has not been previously reported on a maxillary sinus MFH; however, numerous cases involving soft-tissue MFH are reported in the lit-

TABLE

Cases of MFH of the Maxillary Sinus Reported in the Literature

Patient—initial symptoms	Histology	Treatment and follow-up
1. 67 F—pain, swelling of maxillary region × 6 mo. (5)	Storiform and fascicular pattern, +1 stromal atypia, multinucleated atypical giant cells, mitosis 2+, focal inflammatory cells, necrosis	Local excision then radical maxillectomy and orbital exenteration; no recurrence 18 mo later
2. 53 F—long history of slowly progressive swelling of gingiva and cheek (5)	Storiform and fascicular patterns, stromal atypia, multinucleated benign and atypical giant cells, mitosis 3+, invasive into mucosa	Maxillectomy, radiotherapy; no follow-up available
3. 65 F—swelling maxillary region (5)	Storiform pattern, +1 stromal cell atypia, multinucleated benign giant cells, mitosis 1+, invaded muscle and fat	Subtotal local excision; 6 mo later no further therapy given
4. 52 M—mass maxillary region (5)	Storiform, fascicular and myxoid pattern; 2+ stromal cell atypia, multinucleated benign and atypical giant cells; mitosis 2+; focal inflammation, infiltrated bone	Partial maxillectomy, 2 yr later recurrence, radical maxillectomy, orbital exenteration, radiotherapy; 4 yr later alive with locally persistent unresectable tumor, treated with more radiation
5. 54 F—swelling alveolar ridges, loosening of teeth, 2 years (5)	Fascicular pattern 3+ stromal atypia, multinucleated benign and atypical giant cells, mitosis 4+, extensive inflammation, necrosis	Biopsy only, refused further therapy, lost to follow-up
6. 32 F—recent onset proptosis (5)	Storiform fascicular, myxoid patterns, 2+ stromal cell atypia, multinucleated benign and atypical giant cells, mitosis 3+, focal inflammation, invaded bone, focal hemangiopericytoma pattern	Caldwell-Luc procedure; partial resection for diagnosis, multiple metastatic lesions in bone, treated with chemotherapy
7. 23 F—4 mo mass in neck; rhinorrhea, airway obstruction (6)	Mixture of histiocytes, xanthoma cells, and variable numbers of fibrocytes; Touton giant cells; prominent lymphocytic inflammation	Subtotal excision; chemotherapy; 6 mo later left total maxillectomy, orbital exenteration; no recurrence 1 yr later
8. 47 M—tooth extraction; 7 mo later numbness left side of face (7)	Storiform pattern, foam cells, bizarre histiocytes, invaded soft tissue and bone	Biopsy, radiotherapy, 1 mo later left total maxillectomy, orbital exenteration, no recurrence 1 yr later
9. 65 M—pain in cheek (8)	Anaplastic spindle cells in occasional storiform pattern, xanthomatous giant cells, focal inflammation; 10–15 mitoses/HPF, invaded bone	Biopsy, partial maxillectomy, removal floor of orbit
10. 59 M—3 mo left mandibular swelling (9)	Polymorphic fibroblasts in fascicles, storiform pattern, nuclear atypia, foamy histiocytes; occasional giant cells, prominent inflammatory infiltrates, invaded surrounding muscle	Left maxillary resection with ethmoid sinus, orbital exenteration, neck dissection; 2 positive nodes, radiotherapy; dead 6 mo later; at autopsy, no residual tumor
11. 51 F—3 wk right facial swelling (10)	Fibroblasts and histiocytes, storiform pattern, marked cellular pleomorphism, scattered giant cells, numerous mitoses, prominent inflammatory infiltrate	Biopsy then hemimaxillectomy, orbital exenteration, chemotherapy, 1 yr later—local recurrence in hard and soft palate, surgically resected, radiotherapy; no recurrence 2 yr later
12. 53 F—seen for endodontic therapy (11)	Cellular, storiform pattern, moderate nuclear pleomorphism; 3 mitoses/HPF	Caldwell-Luc procedure, local excision followed by right radical maxillectomy, exenteration, no recurrence, 27 mo later
13. 49 F—3 wk epistaxis (12)	Myxoid variety of malignant fibrous histiocytoma	Chemotherapy, subtotal maxillectomy, left radical ethmoidectomy and removal of nasal septum, $2^{1}/_{2}$ yr after presentation, disease free

TABLE—*Continued*

Patient—initial symptoms	Histology	Treatment and follow-up
14. 26 F—long rhinitis; 12 mo left nasal obstruction (12)	Myxoid variety of malignant fibrous histiocytoma	Incomplete removal of tumor; chemotherapy; total maxillectomy; 3 mo later, disease free
15. 32 F—6 wk rhinorrhea, nasal pain (13)	Atypical fibroblasts with focally prominent storiform pattern; focal histiocytes, giant cells, mitosis 2–3/HPF, invaded mucosa and bone	Partial left maxillectomy, radiotherapy chemotherapy, 1 mo later dead; at autopsy, bone and liver metastases
16. 46 M—8 mo nasal obstruction and epistaxis (14)	Storiform pattern; mitosis 0–2/HPF EM; large cell with poor intracytoplasmic filaments, histiocytelike cells—lysosomes, indented nucleus, scanty chromatin, focal, interdigitations; admixed myofibroblasts—spindle shaped with elongated nucleus, bundles of microfilaments	Partial resection then radical surgery (not further specified); 1 mo later disease-free
17. 80 M—30 mo neuralgic pain and numbness right half of face (14)	Storiform pattern, extensive hyalinization, osteoclastlike and bizarre multinucleated giant cells; mitoses 2–3/HPF	Right partial maxillectomy; 2 mo later right ethmoidectomy; 9 mo later recurrent tumor, radical right maxillary sinus resection, right orbital exenteration; 2 mo later residual tumor in right orbital cavity
18. 39 M—sinusitis × 20 yrs, paresthesias, sharp pain left side of face, toothaches left maxilla × 30 mos (15)	Pleomorphic spindle cells in storiform pattern, atypical histiocytes, bizarre giant cells, mitosis	Left maxillary sinusotomy, radiation therapy, chemotherapy, dead 1 yr after onset; at autopsy metastasis to lungs, pleura, pancreas, kidneys, and bone marrow
19. 59 F—5 mo cheek pain, paresthesias of left lip (16)	Spindle cells in storiform pattern, histiocytes intermixed	No surgical treatment, radiotherapy, chemotherapy; dead 5 mo after diagnosis (no autopsy; clinically enlarged cervical lymph nodes)
20. Present case—45 M, several mo nasal obstruction	Haphazardly arranged spindle cells in an occasional storiform pattern; numerous bizarre multinucleated giant cells, few foamy histiocytes; Mitosis 1/HPF	Right maxillectomy, 3 mo later, paranasal sinus CAT scan suggests recurrent tumor

erature (20, 21). The histiocytic markers include alpha$_1$-antitrypsin, alpha$_1$-antichymotrypsin, and lysozyme. Although lysozyme is present in ordinary histiocytes and benign fibrous histiocytomas, it is a poor marker for MFH. By contrast, alpha$_1$-antitrypsin and alpha$_1$-antichymotrypsin have been shown to be excellent markers for MFH with less frequent staining seen in benign fibrous histiocytomas. Other neoplasms that exhibit positivity for alpha$_1$-antitrypsin and alpha$_1$-antichymotrypsin include renal cell carcinoma, Wilms' tumor, and mesotheliomas. Other sarcomas, such as leiomyosarcoma, liposarcoma, and malignant schwannoma, are negative for these two enzymes.

The positive staining in this case for S-100 protein was unusual. S-100 protein was first considered to be specific for Schwann cells and their derivatives. Subsequent studies have revealed this antigen in melanocytes, chondrocytes, myoepithelial cells, Langerhans' cells, interdigitating cells (reticulum cells) of the lymph node and spleen, and sinus histiocytes in massive lymphadenopathy (22, 23). Histiocytes, fibroblasts, and fibrosarcomas are not reported to stain with this enzyme. The explanation for the staining in our case may represent differentiation of the tumor cells toward reticulum cells of the reticuloendothelial system.

The differential diagnoses include anaplastic carcinoma, fibrosarcoma, liposarcoma, and leiomyosarcoma. Although a focal storiform pattern may be seen in any of these neoplasms, it is not as prominent as in MFH. In addition, the associated features of MFH (foamy histiocytes and multinucleated giant cells) are minimally if ever present in other tumors. Features diagnostic for these other tumors, that is, lipoblasts and fascicular or herringbone arrangement of spindle cells, should be thoroughly searched for. Cytochemical stains for glycogen and mucin may be of assistance in determining an epithelial origin. Immunohistochemistry and electron microscopy will further differentiate these other malignancies from MFH.

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Students' Corner

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The Etiology of Primary Spontaneous Pneumothorax

Eugene Dula, M.D., and Richard Konsens, M.D.

Prior to 1932 it was generally accepted that spontaneous pneumothorax (SP) almost always indicated underlying pulmonary tuberculosis. In 1932 Kjaergard reported "Spontaneous Pneumothorax in the Apparently Healthy," which showed that spontaneous pneumothorax (SP) could be diagnosed in patients who had neither signs nor symptoms of tuberculosis, nor any other generalized lung pathology.

SP is currently classified into two distinct etiologic groups. SP occurring in the seemingly healthy person with no apparent or detectable pulmonary disease, currently viewed as a separate condition, will be discussed here. Variously described as idiopathic pneumothorax, pneumothorax simplex, benign pneumothorax, or primary SP, it remains an etiologic enigma despite its prevalence. The incidence in the general population is reported to be about 1 in 11,500; in males 20 to 29 years of age the incidence is 1 in 3000 (1). SP occurs in people with detectable pulmonary disease or trauma, widespread emphysema being the most common cause. This form of SP may complicate a wide variety of lung diseases, such as focal lung lesions (bullae, cysts, abscesses), primary or secondary pulmonary malignancies, or generalized diseases such as emphysema, bronchitis, or asthma. Other known conditions are endometriosis and neurofibromatosis.

The Pulmonary Bleb. Primary SP implies an unknown etiology. The majority of evidence incriminates the rupture of a pulmonary bleb, an air-filled space between the lung parenchyma and the visceral pleura. Because of the lack of a single accepted classification, in this article the terms bleb, bullae, and air-filled cystic lesion are used interchangeably. The most conclusive evidence incriminating blebs as the etiology of primary SP comes from reports of patients with primary SP at thoracotomy, in well over 90% of whom blebs were found on pathologic examination (2, 3).

Cases have also been cited in which blebs were not seen in association with primary SP. Tears of the visceral pleura at the point of attachment of a pleural adhesion or at a focus of subpleural pulmonary fibrosis have also been reported as a possible cause of primary SP (4). Others have suggested that rupture of the elastic fibers in the subpleural alveoli into the visceral pleura can result in separation and elevation of the pleura, causing a tear as air is forced in from the lungs (5). In one report, thoracotomy did not detect any leakage of air although the visceral pleura was elevated by air. This group postulated that free air may have dissected along the interstitial bands of connective tissue of the pleural surface secondary to intrapulmonary rupture of a vesicle or alveolus. Killen and Gobbel suggested that this may represent interstitial pulmonary emphysema with secondary accumulation of air in the intrapleural space (6).

Theories of Congenital Origin. Several theories suggest a congenital component for pulmonary blebs. Congenital bullous emphysema is a form of emphysema that produces large subpleural blebs or bullae. Another congenital theory suggests a developmental anomaly in the lung tissue resulting in the persistence of a peripheral zone of embryonic tissue that fails to differentiate into alveoli and subsequently develops into blebs (7).

Many patients under 40 years of age with primary SP are tall, thin, asthenic types (8–11). Withers and Fishback suggested that the rapid

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growth rate of the lung itself relative to its vasculature in a long, slender lung may cause relative ischemia and resultant bleb formation in the visceral pleura farthest from the main arterial supply, the apex of the lung. They also suggested that within a few years after the growth spurt, but during years of vigorous physical activity such as the third decade of life, wear and tear on these blebs could result in rupture and spontaneous pneumothorax (11). Another paradigm for the occurrence of pneumothorax in young adults with long, narrow chests has been suggested. As lung height increases, volume strain near the apex of the lung rises both relatively and absolutely compared to the base of the lung. The increased strain on the apical lung parenchyma in such a lung could produce blebs in otherwise healthy young adults and the risk of primary SP (9, 10, 12). Clinical studies of patients with primary SP show that its incidence is approximately five to six times greater among men than women (8, 9, 13, 14). The sex association between primary SP and males may simply be a result of the longer, narrower lungs that tall, thin men have compared to women.

Familial spontaneous pneumothorax (FSP) is a rare condition that lends support to the congenital basis of primary SP. A review of the literature identifies 67 individuals in 23 families affected by FSP. In ten families parents and children were affected; four of the families had affected males in successive generations. Affected siblings with unaffected parents were noted in 14 families. There have been no reports on consanguinity (1). Berlin cites 17 families with parent-to-child transmission suggesting that FSP can be dominantly inherited, though not all carriers would necessarily suffer pneumothorax (15). Though no genetic markers have as yet been detected for FSP, the most recent report by Sharpe et al suggests possible linkage between the HLA loci on the sixth chromosome and the locus for FSP (16).

A number of reports document an unusually high incidence of minor anomalies in patients with primary SP, i.e., cervical ribs, anomalous vertebrae, spina bifida, and chest deformities such as pectus excavatum. It has been suggested that some of these patients were not simply thin but actually had muscular hypotrophy, and a few papers have related pneumothorax to the congenital connective-tissue disorders Ehlers-Danlos and Marfan syndromes (17). Metivier and associates studied the lung collagen and proteoglyconated soluble peptides in patients with primary SP, noting modifications of collagen, increases in soluble proteins, and an increase in hydroxyproline content in these lungs. They concluded that abnormalities in the structure or the biosynthesis of collagen might result in increased degradation and resultant rupture causing pneumothorax (18, 19).

Stephenson based the "sharp-rib syndrome" theory on the frequent presence of a sharp inner border of the first or second rib resulting in chronic trauma and primary SP. Over 14 years, 49 patients who underwent operations for SP and had no other pulmonary pathology had their upper ribs palpated intraoperatively, and 28 (57%) were found to have a sharp inner border. He contrasts this result with 100 patients who underwent thoracotomy for conditions other than pneumothorax, of whom only eight (8%) were found to have a sharp rib (20).

Theories of Acquired Origin. Many reports propose a wide variety of acquired factors as predisposing to primary SP. For example, hyperdistention of apical areas of the lung with performance of the Valsalva maneuver is documented. With repeated efforts such selective distention may ultimately result in blebs (5, 11). It has also been suggested that temporary atelectasis could cause local ventilatory obstruction leading to both compensatory emphysema and ischemia of the visceral pleura. As a result, alveoli might rupture, permitting air to enter the pleural space. This theory has been supported by the occasional appearance of concurrent mediastinal emphysema and SP (21).

Whereas the incidence of secondary SP increases with age (9), primary SP peaks in young adulthood and then declines with age. The percentage of patients under 40 years of age is usually high; reports of 75%–90% are common (8, 10, 13, 14). West suggested that changes in lung compliance with increasing age may decrease some of the apical stress thought to lead to the formation of blebs and thus decrease the incidence of primary SP with advancing age (14a).

Patients with primary SP smoke considerably more than healthy people. In O'Hara's study only 7 of 164 patients with primary SP were nonsmokers, and 54 smoked more than two packs per day (14). Hangrinsson's major study in Iceland revealed that 90% of his cases of primary SP were smokers (13). Though it is difficult to associate a condition commonly seen in young people with chronic exposure to cigarette smoking, it is possible that heavy smoking is an important element in the etiology of primary SP (22). The chronic bronchitis and persistent cough due to smoking often noted in patients with primary SP may traumatize the previously existing apical blebs by one mechanism or another, eventually resulting in rupture.

Little evidence supports the concept that strenuous physical exertion may precipitate rupture of an emphysematous bleb producing SP. On the contrary, a number of researchers have observed an increased incidence of primary SP among those with sedentary life patterns, thus suggesting the possibility that primary SP is often a complication of long-standing alveolar hypoventilation (14, 23).

Though primary SP occurs in patients without apparent pulmonary pathology, both prior SP and prior pneumonia are frequently reported. In O'Hara's study of 164 patients with primary SP, 38 had documented previous pneumothorax and 14 had a prior history of pneumonia. This correlates well with theories that a bleb may result from an area of inflammatory scarring (22). Other theories about the origin of the bleb are that it is secondary to pulmonary ischemia (24) or that it arises from unfavorable ventilation-perfusion quotients of the apical pulmonary regions, marked negative pleural pressure, or various noxious agents (25).

Pathology. On gross observation during thoracotomy, blebs occur at the apical regions of the lung and are seen in almost all cases of primary SP. They may be either single or multiple and range from 0.2 cm to 2 cm in diameter, with pinhole-sized leaks consistently found. The surrounding areas are fibrosed and thickened, making the entire lesion approximately 3 cm in diameter. Fibrotic adhesions from lung to pleura were reported with variable frequency. In cases that failed to heal within 48 hr of chest tube drainage, more substantial tears were often found. Characteristically, the remainder of the lung appeared normal (3, 13).

Microscopic observations of lungs with primary SP have been nonspecific. As on gross observation, both cysts and emphysema are observed microscopically. Both destructive and compensatory emphysema are found. The cysts themselves are lined with fibrous tissue, surrounded by fibrosed pleura, and in some instances mesothelial cells are prominent. Emphysematous changes are also seen scattered between the fibrotic areas. Dense subpleural scarring is noted, as is fibrosis of the lung parenchyma itself. Atelectatic foci that are invaded by fibrous tissue are also common and are related to adjacent areas of compensatory emphysema.

Chronic inflammation, consisting of lymphocytes, plasma cells, and macrophages, of the dense scar tissue are occasionally observed as are calcifications in the area of the blebs. No other specific inflammatory or occlusive lesions of the vasculature are noted though endarteritis obliterans is common, though unexplained.

In summary, the gross and microscopic findings of these studies suggest that primary SP is characterized by bleb formation, often appearing as a postinflammatory disorganization, possibly due to a nonspecific infection. This constant relation of blebs to scar tissue supports the hypotheses that primary SP is not congenital, though this is certainly not conclusive evidence (3, 13, 26).

More recently, the bleb has been studied with the electron microscope. Studying the lungs of patients with primary SP, Tueller et al observed an increase in alveolar septal mass, compared to normal lungs, in the area immediately adjacent to the point of apical rupture. They noted a proliferation of the alveolar basal lamina characterized by abundant collagen, dense elastic fibers, and both Type I and Type II epithelial cells. Similar increases in interstitial macrophages and proliferation of epithelial cells have been reported as responses to pulmonary stress and/or insult such as oxygen intoxication, ozone or nitrogen exposure, and the inhalation of cadmium salts, and are also seen in the adult respiratory distress syndrome (27).

Using the scanning electron microscope, Ohata and Hiroshi have also studied pulmonary blebs, typing them by appearance according to the Reid classification (26). The Reid Type I cyst consists of a small amount of greatly distended lung that is demarcated from normal lung tissue by a long, narrow neck. The Reid Type II cyst is a shallow, wide layer of overdistended lung parenchyma. The surface of the Reid I cysts has a remarkable sparsity or even total lack of mesothelial cells causing a thin surface, resulting in naked, uncovered collagen fibers along with pores and crevices through the thinned walls. At the base of the cyst the walls are flat and composed of amorphous material interspersed with pores. In contrast, the mesothelial cells on the surface of the Reid II cysts are well preserved, though focal areas of sparseness are noted. Also, the base of Reid II cysts shows some deterioration of pulmonary alveoli that were exposed to the bullous space. It appears reticulated and trabeculated with an increase in alveolar Type II cells.

Large ballooning giant bullae not complicated by SP were also examined by Ohata and Hiroshi and reported for comparison (26). The surface of these bullae was normal, containing normal mesothelial cell layers without crevice formation, and with thick walls devoid of pores. At the base of these bullae, however, deterioration even greater than in Reid II cysts with multiple trabecular structures was apparent.

A difference has been noted in the quantity of the pleural mesothelial cells observed in blebs associated with SP and those not associated with SP. Ohata and Hiroshi suggest that these mesothelial cells may play a role in the pathogenesis of primary SP (26). Masshoff and Hofer theorize that the mesothelial cells in an affected area proliferate to form a bleb in response to the leakage of air (28). The direct communication between lung parenchyma and bullae is also proven in this study, which demonstrates that air can leak through the walls of bullae into the pleural cavity under certain conditions without rupture of the bullae. Nevertheless, the findings of the Reid I bleb in conjunction with Masshoff's findings of mesothelial proliferation upon exposure to air still do not fully explain the sequential pathogenesis of bleb formation and rupture.

The evidence supports six congenital factors as associated with the development of primary SP: sex: male 85%; persistence of embryonic tissue resulting in blebs; body habitus; familial spontaneous pneumothorax; sharp-rib syndrome; connective tissue disorders.

Five noncongenital factors are associated with primary SP: Valsalva maneuver; smoking; sedentary life-style (alveolar hypoventilation); seasonal respiratory infection; gross and microscopic appearance resembling various inflammatory states.

From the number and variety of theories it is clear that no single explanation is definitive. Moreover, the term "primary spontaneous pneumothorax" itself reflects lack of knowledge. As information accumulates, it is possible that all cases of primary SP will eventually be attributed to secondary causes.

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Correction

In the article in the May 1985 issue by Murrel H. Kaplan, M.D., FACG, “Stress, Pancreatic Perfusion, and Acute Pancreatitis: A Unified Concept of Pathogenesis,” the sentence on page 328, column 2, beginning on line 17 should have read: “Its excitation results in splanchnic vasoconstriction, hypoperfusion, ischemia, and hypoxia.”

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Cardiac Problems in Elderly Patients: Early Recognition and Management

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Volume 52
Number 8
October 1985

CONTENTS

CARDIAC PROBLEMS IN ELDERLY PATIENTS: EARLY RECOGNITION AND MANAGEMENT

Introduction *Morris Kleinfeld, M.D.* 579

Hypertension in the Elderly *Jaime Uribarri, M.D., Man S. Oh, M.D., and Hugh J. Carroll, M.D.* 581

Valvular Heart Disease in the Elderly *Neil D. Berman, M.D., FRCP(C)* 594

Cardiac Arrhythmias in the Elderly: Selected Aspects *Martin Dolgin, M.D.* 601

Sinus Node Dysfunction: New Concepts and Evaluation of Patients with Suspected Sick Sinus Syndrome *J. Anthony Gomes, M.D.* 610

The Role of Early Radionuclide Ejection Fraction in Predicting Early Mortality after Acute Myocardial Infarction in the Elderly *Stephen J. Green, M.D., Lawrence Y. Ong, M.D., Peter Reiser, M.D., and John Morrison, M.D.* 618

The Management of Depression and Anxiety Following Myocardial Infarction *Theodore A. Stern, M.D.* 623

Noncardiac Surgery in the Elderly Patient with Heart Disease *Richard F. Grady, M.D.* 634

GENERAL ARTICLES

Glyburide-Induced Hypoglycemia in an Elderly Patient: Similarity of First-Generation and Second-Generation Sulfonylurea Agents *Terry H. Edwards, M.D., Glenn D. Braunstein, M.D., and Mayer B. Davidson, M.D.* 644

continued

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CONTENTS *continued*

Gastric Neurilemmoma: Case Report *Altino da Silva Pinto, M.D. and Julio A. P. Novo, M.D.* 647

SPECIALTY NOTES

ENVIRONMENTAL MEDICINE *Alf Fischbein, M.D., editor*

Cardiotoxic Effects of Chemicals *Steven F. Horowitz, M.D., FACC, Deborah Matza, RN, and Josef Machac, M.D.* 650

RADIOLOGY *Jack G. Rabinowitz, M.D., editor*

Case Report: Ultrasonographic Features of "Milk of Calcium" in Kidney *Evangelos Diakoumakis, M.D., Ulrick Vieux, M.D., Burton Seife, M.D., and Thomas C. Snyder, M.D.* 656

Case Report: Milk of Calcium in the Kidney after Cyst Puncture *Peter H. Tey, M.D., Afzal Ahmed, M.D., and K. F. Chan, M.D.* 659

SURGERY

Gastric Inflammatory Pseudotumor *Kent E. Skogerson, M.D., Allen J. Fredland, M.D., and Mohan C. Airan, M.D.* 661

STUDENTS' CORNER

Senile Macular Degeneration and Kuhnt-Junius Degeneration as Separate Entities: Review *Mark Levitan, M.D., George M. Gombos, M.D., Harvey Levitan, M.D., and Lawrence J. Levitan, M.D.* 663

Coombs' Positive Hemolytic Anemia following Sulfasalazine Therapy in Ulcerative Colitis: Case Reports, Review, and Discussion of Pathogenesis *Jeffrey I. Mechanick, M.D.* 667

Letter 671

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 52, No. 8, October 1985
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Cardiac Problems in Elderly Patients: Early Recognition and Management

Introduction

The importance of cardiac disease in the elderly population in the Western world has been growing; cardiac disease is now the primary cause of death in this subset of the population. Physicians in all disciplines find themselves having to deal increasingly with a variety of cardiac disorders in older persons. In response to a growing need for earlier recognition and improved management of these disorders, intensive basic and clinical research has accumulated, as witnessed by the proliferation of articles in a variety of journals both here and abroad.

A broad, sweeping view of geriatric cardiology was not the intent of this special symposium, although general concepts are invoked as the basis for discussions of particular topics. Subjects were chosen because of their relevance to early detection and management of heart disease in the elderly patient.

Advances in our knowledge of cardiac electrophysiology and pacing techniques have been so rapid in recent years that authority on the subject is needed. Dr. Gomes' paper on sinus node dysfunction, new concepts and evaluation of patients for permanent pacing, encompasses several aspects of this progress and updates our knowledge in this specialized field.

As ongoing research provides new rationales for the management of such diverse problems as hypertension, valvular heart disease, and ischemic heart disease, the need grows for amplification and continuing education of the practicing physician. These areas are examined in the papers "Hypertension in the Elderly" by Drs. Uribarri, Oh, and Carroll, "Valvular Heart Disease" by Dr. Berman, and "Early Risk Factors in Acute Myocardial Infarction" by Drs. Green, Ong, Reiser, and Morrison.

As clinical electrocardiography has evolved, its application to the elderly cardiac patient has been well recognized. The recent use of continuous ambulatory monitoring in the detection of a number of cardiac arrhythmias and conduction disturbances, and the use of HIS bundle recording as clarification, have provided a basis for more concise management of these disorders. HIS bundle recording has become the definitive tool for differentiating ventricular tachycardia from supraventricular tachycardia with aberrancy. An excellent analysis of the state of the art of clinical electrocardiography is provided by Dr. Dolgin in his paper on the recognition and management of arrhythmic disorders in the elderly.

The subject of heart surgery, with particular emphasis on the indications and the different prognoses pertaining to the various valvular disorders, is dealt with in the paper by Berman. An often-neglected topic in the management of coronary artery disease and acute myocardial infarction is addressed in Dr. Stern's paper, "The Management of Depression and Anxiety following Myocardial Infarction." Dr. Stern recognizes that psychological risk factors are implicated in the genesis of a variety of cardiac disorders, including myocardial infarction. He provides substantive data for the need to consider psychiatric intervention in those patients who manifest anxiety and depression in the course of myocardial infarction. Assessing operative risks in the elderly cardiac patient undergoing noncardiac surgery requires balancing the benefit to the patient against the risk of the surgical procedure. Dr. Grady, in his paper "Noncardiac Surgery in

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the Elderly Cardiac Patient," addresses this topic and provides a multifactorial assessment of perioperative risk.

A More Aggressive Approach. In several papers in this symposium there are two implied assumptions. The first is the need for a more aggressive approach to the various cardiac disorders in the elderly. There is ample evidence that the patient's quality of life may be greatly enhanced by such a change in attitude. Surgical correction of aortic and/or mitral valve disorders, permanent pacemaker implantation in patients with sick-sinus disease, vigorous management of various hypertensive disorders and congestive heart failure are just a few examples of conditions in which a more aggressive approach has proved effective in improving the quality of life of the elderly person.

A Holistic Approach. The second implication is the reflection that since the elderly cardiac patient is often simultaneously afflicted with groups of concommitant disorders such as cerebrovascular disease, constipation, diabetes mellitus and its complications, urinary incontinence, and insomnia, it is sound medical practice to take a holistic approach and deal with the cardiac patient in the context of his or her total physical and psychological situation. Several of the authors in this issue take recognition of this important concept.

All the papers in this symposium were originally delivered orally at the Seventh Annual Geriatric Seminar on Recognition and Management of Selected Cardiac Problems in the Geriatric Patient, held on June 19, 1984, and sponsored by the Department of Long-Term Care Medicine of the Kingsbrook Jewish Medical Center, Brooklyn, NY.

As the program chairman of the seminar and the editor of this symposium, I have been fortunate to assemble a group of highly qualified authorities to provide the reader with the latest developments in their respective fields. I am grateful to them for their contributions.

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Hypertension in the Elderly

JAIME URIBARRI, M.D., MAN S. OH, M.D., AND HUGH J. CARROLL, M.D.

As the elderly represent a continuously increasing proportion of the population, so do their medical problems, and prominent among these problems is hypertension. It is our purpose here to consider the epidemiology, pathophysiology, and clinical aspects of hypertension as they relate to older subjects, defined for the purposes of this article as those over 60 years of age.

Epidemiology

That hypertension is an important risk factor for cardiovascular mortality in all ages (1) and that the incidence of hypertension increases linearly with age (2) have been thoroughly documented and long appreciated. Data from the National Center for Health Statistics (3) indicate that 40% of white subjects aged 65–74 years and more than 50% of blacks in the same age group have systolic blood pressure in excess of 160 mmHg, a diastolic pressure in excess of 90 mmHg, or a combination of systolic and diastolic hypertension.

A salutary effect of antihypertensive therapy in the elderly has not been extensively documented, but several studies, including the VA cooperative study (4) and the Hypertension Detection and Follow-Up Program (5), provide data that support the value of attempting blood pressure reduction in the elderly.

Pathophysiology

The large arteries are normally distensible and elastic. When the heart ejects a bolus of blood into the arterial bed, the pressure in the arteries rises to a level determined by the cardiac output and the compliance of the arteries. The elastic recoil of the arteries during diastole supports a pressure that diminishes as blood is forced through the arterioles and into the capillaries where the exchange of metabolites takes place. The major determinants of the pressure within the arterial bed are the cardiac output (CO) and the resistance to flow through the peripheral arterioles (total peripheral resistance, TPR). With appropriate units the following equation defines the blood pressure (BP):

$$\mathrm{BP} = \mathrm{CO} \times \mathrm{TPR}$$

BP here is mean arterial pressure (MAP), arrived at by integrating the areas under the curves of systolic and diastolic pressures on an oscilloscope. It can be fairly estimated as diastolic pressure plus one-third of the pulse pressure (difference between systolic and diastolic pressures). For a variety of purposes, the "upper limit of normal" MAP is usually set at 107–110 mmHg.

The cardiac output is calculated as the product of stroke volume and heart rate, but ultimately it depends on venous return to the heart. One factor of obvious importance in determining venous return is the blood volume, which, in turn, depends to some extent on body salt content.

Peripheral resistance may be influenced by a variety of mechanisms, as follows:

- Sympathetic nervous system
- Autoregulation
- Increased responsiveness to stimuli (high intracellular content of Na and Ca)
- Angiotensin II
- Structural changes in arteriolar wall

Both catecholamines and angiotensin II are potent arteriolar constrictors. It has been shown experimentally (6, 7) that the response of blood vessels to these agents is increased as the salt content of the vessel wall increases, and some

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evidence suggests that excess salt may similarly influence peripheral resistance in humans (8).

The role of calcium in the control of peripheral resistance in hypertension is unclear. On the one hand, the vascular smooth muscle cannot contract without the action of intracellular calcium (9), and it has been postulated that if salt enhances arteriolar tone, it does so by increasing cellular calcium content (10). Hence the rationale for the treatment of hypertension with agents that inhibit cell calcium uptake (11). On the other hand, several studies of dietary influences on blood pressure have suggested that a calcium-deficient diet is common in hypertension (12, 13), and that supplemental calcium may be of benefit in reducing blood pressure (14). This question awaits resolution, but at present the therapeutic efficacy of calcium channel blockers seems far better supported than that of dietary calcium supplementation.

Autoregulation of blood flow is a mechanism by which arteriolar tone increases or lessens in order to maintain a constant flow through the tissues. Each organ system autoregulates independently, some, especially the brain, more effectively than others. In the case of hemorrhage or excessive diuresis, for example, perfusion of the brain is maintained better than perfusion of the skin. A rise in cardiac output, with overperfusion of all the tissues, would be met by a generalized increase in peripheral resistance, which would have the effect of reducing cardiac output toward or to normal.

Persistent hypertension leads to structural changes in the arteriolar wall, well described by Folkow (15). These changes have been shown to be at least in part reversible if normotension is achieved and maintained (16).

A great deal of information of pathophysiologic and therapeutic importance can be gained by consideration of the baroreceptor reflex, a mechanism whose purpose is to prevent, in the short term, severe fluctuations in blood pressure (Table 1, Fig. 1). A rise in pressure causes impulses to travel over the ninth and tenth cranial nerves to the brain stem, which responds by stimulation of the vagus and inhibition of the nearby sympathetic nuclei. The total effect of the efferent limb of the reflex consists of the following: reduction in heart rate and contractility; relaxation of the arterioles and the capacitance (venous) bed; reduction in the renal production of renin and hence of angiotensin II and aldosterone. When blood pressure falls acutely, the vagus is inhibited and the sympathetic nervous system is stimulated; heart rate and contractility increase, arteriolar tone increases, veins constrict and increase venous return to the heart, and release of renin from the kidneys is increased.

TABLE 1

Classification of Antihypertensive Drugs by Mechanisms of Action

1. Diuretics
    Reserpine
    Methyldopa
    Guanethidine
    Ganglionic blockers
    Clonidine
    Beta blockers
    Ca channel blockers
2. Methyldopa
    Clonidine
    Guanabenz
3. Ganglionic blockers
4. Guanethidine
    Guanadrel
    Reserpine
    Methyldopa
5. Alpha blockers
    Prazosin
    Labetalol
6. Hydralazine
    Minoxidil
    Nitroprusside
    Diazoxide
7. Ca channel blockers
    Nifedipine
    Diltiazem
    Verapamil
8. Antirenin agents
    Reserpine
    Methyldopa
    Guanabenz
    Clonidine
    Guanethidine
    Guanadrel
    Ganglionic blockers
    Beta blockers
9. Converting-enzyme inhibitors
    Captopril
10. Angiotensin II inhibitor
    Saralasin

Angiotensin II increases blood pressure not only by directly inducing contraction of arteriolar smooth muscle, but also by stimulating the sympathetic nervous system, and, in the long term, by inducing salt retention through stimulation of aldosterone production (Fig. 2.).

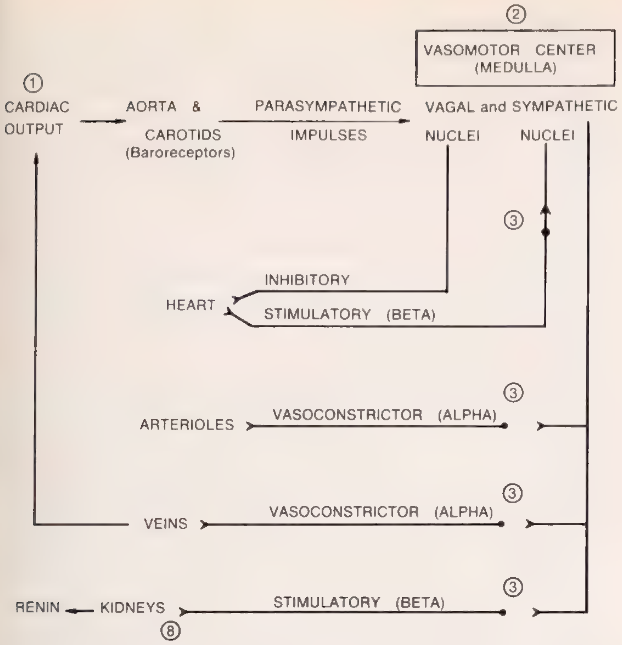
The mean arterial pressure (MAP), calculated as diastolic pressure plus one-third of the pulse pressure, is determined by cardiac output and peripheral resistance. However, the levels of pressure attained in systole and diastole may vary widely for a given MAP. For example, a MAP of 100 mmHg might represent a wide pulse pressure, 160/70, or a narrow pulse pressure, 120/90. Pulse pressure is wider when the large arteries are more rigid and when the stroke volume is large.

Effects of Aging on the Cardiovascular System

Blood volume is lower in the elderly (17). The reduced volume increases the hazards of overdiuresis.

Plasma renin activity tends to decrease (18) and plasma norepinephrine levels to increase (19).

The number of beta-adrenergic receptor sites diminishes (20); a comparable decrease in alpha receptors has not been demonstrated (21).


①
CARDIAC OUTPUT
AORTA & CAROTIDS (Baroreceptors)
PARASYMPATHETIC IMPULSES
②
VASOMOTOR CENTER (MEDULLA)
VAGAL and SYMPATHETIC
NUCLEI
NUCLEI
③
INHIBITORY
HEART
STIMULATORY (BETA)
③
ARTERIOLES
VASOCONSTRICTOR (ALPHA)
③
VEINS
VASOCONSTRICTOR (ALPHA)
③
RENIN
KIDNEYS
⑧
STIMULATORY (BETA)

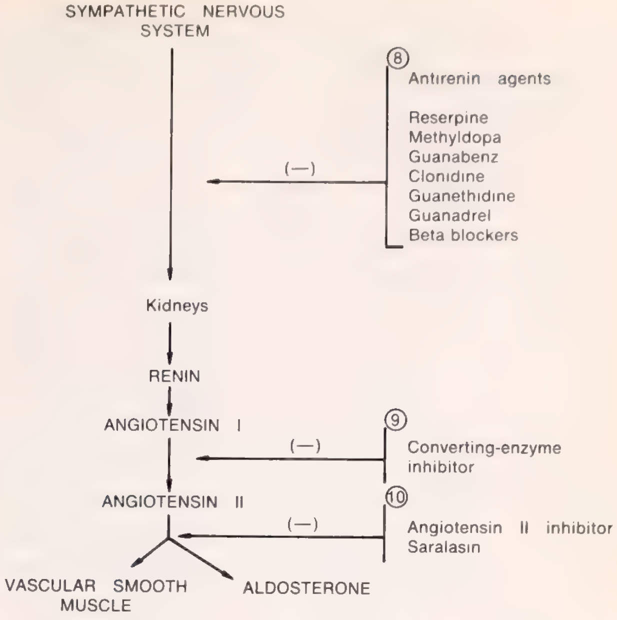

SYMPATHETIC NERVOUS SYSTEM
⑧
Antirenin agents
Reserpine
Methyldopa
Guanabenz
Clonidine
Guanethidine
Guanadrel
Beta blockers
(−)
Kidneys
RENIN
ANGIOTENSIN I
⑨
(−)
Converting-enzyme inhibitor
ANGIOTENSIN II
⑩
(−)
Angiotensin II inhibitor
Saralasin
VASCULAR SMOOTH MUSCLE
ALDOSTERONE

Fig. 1. Left The baroreceptor arc. Numbers 1, 2, 3, and 8 refer to drug classes in Table 1.

Fig. 2. Right The renin-angiotensin system: pharmacologic inhibition. Numbers 8, 9, and 10 refer to drug classes in Table 1.

Cardiac output diminishes at rest (22) and in response to exercise (23), even in the absence of obvious heart disease.

Progressive stiffness of the aorta and large arteries tends to produce a disproportionate increase in systolic pressure. If vascular rigidity were the sole factor affecting the hemodynamics, the mean blood pressure would be normal, and hence the diastolic pressure would decrease in proportion to the rise in systolic pressure. Increased rigidity of the aorta and carotids also diminishes the effectiveness of the baroreceptor reflex (24), a phenomenon frequently observed in the elderly.

Effects of Aging, Hypertension, and Vascular Disease

Morbidity and mortality from hypertension in the elderly are due to effects on the heart and blood vessels. In both tissues the changes caused by hypertension are superimposed upon those of senescence (25, 26), and it is difficult to distinguish among the changes of senescence, arteriosclerosis, and hypertension. Changes attributable to hypertension in arterioles and small arteries consist of hypertrophy and hyalinization of the media; thickening, fraying, and duplication of the internal elastic membrane; thickening of the intima; and fibrosis of the adventitia. The vascular changes of senescence include reduced elastin and increase in collagen and in the cross-linkage of collagen.

Chobanian has proposed (27) that this vascular aging may be the result of chronic hemodynamic stresses on the vessel wall and could be inhibited by chronic reduction in blood pressure to below "normal" levels. Normotensive rats treated for a year to maintain their systolic blood pressure below 110 mmHg showed minimal or total absence of the arterial changes expected from their advanced age. It is possible, then, that even normal blood pressure levels are high enough to accelerate the vascular aging process.

In the larger arteries the pace of atherosclerosis is increased by hypertension (28). The hazards are those imposed by gradual loss of blood supply to tissues as their small vessels close and catastrophes caused by acute rupture, thrombosis, or embolic closure of major vessels.

Cerebrovascular Disease. Disease of the cerebral vessels leads to a variety of effects, including major stroke due to thrombosis, embolism, or hemorrhage. Hemorrhage is usually attributed to rupture of Charcot-Bouchard aneurysms (29), deformities caused by rupture of the media of cerebral arterioles. In addition to major thromboses, transient ischemic episodes, cerebral atrophy, and lacunar states are encountered. Lacunae (30) are very small infarcts found in the internal capsule, putamen, thalamus, and pons but not in the cortex or spinal cord. They produce a number of syndromes which vary with locations: internal capsule, hemiplegia without sensory changes or aphasia; thalamus, pure sensory stroke with paresthesias; pons, dysarthria, and the "clumsy-hand" syndrome. Patients with cerebrovascular disease may also manifest dementia, parkinsonism, and pseudobulbar palsy.

Heart Disease. With advancing age the cardiac output declines and the left ventricular mass increases (22). Fibrosis and amyloid deposition occur independent of vascular disease, at least in part. The valves stiffen and the ratio of capillary flow to muscle mass diminishes. Myocardial compliance diminishes secondary to myocardial stiffness. The superimposition of hypertension not only accentuates the myocardial disease but also accelerates atherogenesis (31) in the coronary arteries. Left ventricular decompensation (Fig. 3) and myocardial infarction are commonplace (32).

Kidney Disease. Renal function in the elderly deteriorates independently of vascular disease (33). The number of glomeruli diminishes, as do renal blood flow, glomerular filtration rate, and renal cortical mass. Deterioration of renal function is increased with the superimposition of the vascular changes of hypertension (34). The frequent occurrence of hypertension associated with atherosclerosis of the aorta and renal arteries is well known.

On the Question of "Systolic Hypertension"

When the large arteries become rigid, the pressure during systole is very high, and the blood is forced so rapidly out of the arterial bed that the pressure in the system has fallen sharply by the time the next bolus of blood enters the arteries. In addition, there is little elastic recoil of the stiff aorta to support pressure during diastole; as a consequence of vascular stiffness, therefore, diastolic blood pressure is lower than normal and pulse pressure is high (35). The vessels of the elderly become rigid because of an increase in collagen and a decrease in elastin content; this phenomenon is frequently enhanced by the presence of severe atherosclerosis. As a result, wide pulse pressure and "systolic" hypertension are common with advancing age (36).

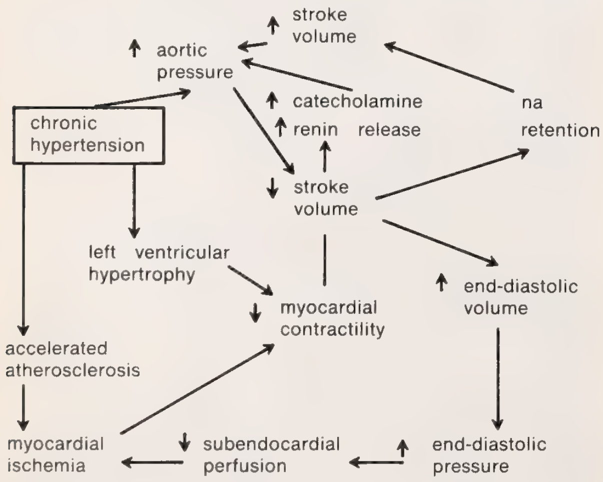


Fig. 3. Mechanisms leading to heart failure in chronic hypertension. Adapted from Cohn JN, Limas CJ, Guiha NH (32).

Many misconceptions have arisen about what is termed "systolic hypertension," and some clarification is useful. Systolic hypertension is usually defined as elevated systolic blood pressure with normal diastolic pressure (37), but this definition is not satisfactory in the absence of agreement about what constitutes a normal systolic or diastolic blood pressure. If we use figures commonly assigned to the elderly, 160 mm Hg for normal systolic and 90 mmHg for normal diastolic pressure, most physicians might agree that a blood pressure of >160/<90 mmHg (for example, 204/84) would represent "pure" systolic hypertension. A patient with such a blood pressure, however, does not have pure systolic hypertension; his MAP is 124 mmHg, and if his cardiac output is normal (or low), then according to the equation BP = CO × TPR, his peripheral resistance is elevated.

The common misconception that peripheral arterial resistance determines the diastolic blood pressure and cardiac output the systolic blood pressure underlies this misinterpretation of "pure" systolic hypertension. If the patient with a MAP of 124 had a blood pressure of 164/104, he might be regarded as having a high peripheral resistance; in fact, the patients with blood pressures of 204/84 and 164/104 mmHg could have the same cardiac output and peripheral resistance, a difference in vascular rigidity explaining the difference in pulse pressure: the more rigid aorta of the patient with a blood pressure of 204/84 has caused the systolic pressure to rise and the diastolic pressure to fall into the "normal" range.

If the term "pure systolic hypertension" is not to be abandoned, perhaps it should be reserved for persons with normal mean arterial pressure, and high systolic and low diastolic blood pressures; for example, those with increased stroke volume or decreased vascular elasticity as the only alterations in hemodynamics.

While altered structure of vascular walls and atherosclerosis are common causes of increased systolic pressure in the elderly, another important cause of diminished large-vessel distensibility is high diastolic blood pressure (38). Because the blood vessels are not made of perfectly elastic materials, blood vessels that distend tend to lose distensibility with rising diastolic pressure. The reduced distensibility in this case is therefore reversible, and when diastolic pressure is reduced, distensibility is restored. This reversible loss of arterial distensibility explains the progressive rise in pulse pressure with rising blood pressure. It would not be uncommon, for example, for a blood pressure of about 150/100 mmHg (pulse pressure 50) to rise to 250/150 mmHg (pulse pressure 100) with loss of therapeutic control. Since this rise in pulse pressure is predictable, we do not consider 250/150 mmHg as representing systolic hypertension; that is, we do not consider the systolic blood pressure disproportionate. A blood pressure of 200/100 mmHg, however, would be considered to represent disproportionately high systolic and pulse pressure for that level of diastolic pressure. Koch-Wesser (39) has proposed that the term "disproportionate systolic hypertension" be used when systolic pressure is greater than twice the value of diastolic pressure minus 15 mmHg. This definition accounts for the progressive rise in pulse pressure with rising diatolic pressure.

Clinical Evaluation of the Elderly Hypertensive Patient

The diagnosis of hypertension should be confirmed by repeated measurements of blood pressure. Pseudohypertension should be considered in an elderly population; the stiffness of the arteries, by increasing the cuff pressure needed to collapse them, may falsely increase blood pressure by a significant extent. Pseudohypertension (40) should be particularly considered in the presence of high blood pressure without any evidence of end-organ damage, or in patients who manifest significant weakness or dizziness not correlated with the height of blood pressure while on treatment.

Auscultatory gap (41) is avoided by inflating the cuff rapidly to 250 mmHg or at least 30 mmHg higher than the palpable point of brachial artery occlusion.

The arm on which blood pressure is being measured should be elevated to the level of the heart. Blood pressure should be measured in both arms in the supine and standing positions.

The possibility of secondary or curable hypertension should always be considered during the initial evaluation of a patient. The differential diagnosis of secondary hypertension may be accomplished in most instances through the history, physical examination, and a few screening tests.

History

Characteristics of the Hypertension. The history should elicit all available information in the following areas: the duration of hypertension, therapeutic regimens, degree of control, and side effects of medications.

Serious consideration should be given to the possibility of renovascular hypertension when moderate to severe hypertension commences after the age of 50, when control of hypertension suddenly becomes more difficult, or when the patient has Grade III or IV retinopathy.

Substances That May Cause Hypertension. Estrogens, corticosteroids, and sympathomimetic agents, the latter frequently present in over-the-counter medications, may cause or worsen hypertension.

Dietary History. Dietary history should include sodium intake and total caloric intake, as well as the patient's attitude toward sodium intake.

Social and Sexual History. Cigarette smoking (42) is an important risk factor, independent of hypertension, for cardiovascular disease.

Heavy alcohol intake is clearly associated with higher mean blood pressures (43). Regular exercise (aerobic) may be a protective factor against cardiovascular morbidity (44).

Since sexual complaints are common side effects with most antihypertensive agents, it is important to establish baseline sexual function before treatment commences.

Concurrent Conditions Known to Be Associated with Hypertension. History of trauma to the abdomen prior to the development of hypertension suggests the possibility of renovascular origin.

Many renal diseases, including those due to collagen vascular diseases such as lupus, scleroderma, and polyarteritis nodosa, may cause hypertension.

Family History. The occurrence of hypertension in other family members does not help to distinguish secondary from essential hypertension. However, a family history of premature cardiac or cerebrovascular disease or death may increase the importance of treatment of even mild hypertension.

The importance of familial conditions associated with hypertension such as pheochromocytoma and hereditary renal disease is greater in the young but not to be neglected in those over 60 years old.

Symptoms of Pheochromocytoma and Hyperaldosteronism. About half of the patients with pheochromocytoma have a history of paroxysms of tachycardia, sweating, and tremor; such a history demands that a screening test for this condition be performed.

Manifestations of hypokalemia in mineralocorticoid-induced hypertension are variable and nonspecific.

Evidence of Target Organ Damage. The heart, brain, kidneys, eye, and major arteries are the target organs, and the signs and symptoms are those of vascular disease: myocardial ischemia and heart failure; cerebral ischemic episodes and strokes; renal insufficiency due to large- or small-vessel disease; and claudication. Retinal findings in hypertension are well known, and visual acuity is altered only when ischemic and hemorrhagic lesions are strategically placed so as to involve such critical structures as the central retinal artery or the macula.

Physical Examination

The object of the physical examination is to assess the severity of hypertension, signs of target organ damage, and evidence of secondary hypertension.

Enlarged kidneys may suggest polycystic disease, and neurofibromas and café-au-lait spots suggest pheochromocytoma. Abdominal bruits are common in the elderly, but when they appear in diastole as well as in systole and when they radiate to the flanks, their presence is suggestive of renovascular stenosis. Abdominal aortic aneurysms commonly involve the renal arteries. True systolic hypertension (with decreased diastolic pressure) may have as its cause such detectable entities as aortic insufficiency, A-V fistula, or Paget's disease. Physical evidence is often recognizable for Cushing's syndrome, hypo- and hyperthyrodism, and collagen vascular disease. The assessment of target organ damage requires careful funduscopic examination, neurologic examination, and examination of the heart, lungs, and peripheral pulses.

Laboratory Data

Careful history and physical examination will have excluded, for practical purposes, all but a few causes of secondary hypertension, such as renal disorders, including parenchymal renal disease and renovascular stenosis, and endocrine disorders—some cases of pheochromocytoma; mineralocorticoid excess; primary aldosteronism; and primary hyperparathyroidism.

All these disorders, except pheochromocytoma and renovascular hypertension, will be excluded by the findings of normal urinalysis and normal serum levels of urea, creatinine, potassium, and calcium. The recommended set of diagnostic tests is completed by the ECG, chest X ray, serum lipids, and glucose.

Pheochromocytoma. Screening for pheochromocytoma in elderly patients with sustained diastolic hypertension should be performed only if one or more of the following conditions is present: severe hypertension, marked fluctuations in blood pressure, presence of orthostatic hypotension in the untreated patient, presence of certain neurocutaneous lesions, and family history of pheochromocytoma.

In these patients a 24-hr urine collection for metanephrine measurement should be obtained; if the test is negative and it has been performed by a reliable laboratory, no further workup is necessary (45).

Renovascular Hypertension. Screening for renovascular hypertension should be performed in the following subgroups:

- Onset of diastolic hypertension after age 50.
- Presence of abdominal bruits radiating to flanks or the presence of a bruit in the diastolic phase of the cardiac cycle.
- Severe hypertension with grade III or IV retinopathy (46).
- Hypertension suddenly out of control despite compliance with prescribed treatment.

Screening for renovascular hypertension consists of a set of tests which varies from one institution to another with the degree of success that institution has had in correlating its screening results with the diagnostic arteriogram. Screening tests include measurement of plasma renin activity in a peripheral vein (47); saralasin infusion test for reduction in blood pressure and elevation in plasma renin activity (48); captopril stimulation of plasma renin activity (49); rapid sequence IVP (50); digital subtraction angiogram (51); and radioisotope renogram (52).

If the screening tests are sufficiently suggestive, arteriography is performed, and plasma renin activity is measured in the separate renal veins; elevation of plasma renin activity on the side of the stenosis and suppression of plasma renin activity on the other side strongly suggest renovascular hypertension (47).

An exhaustive treatment of renovascular hypertension is outside the scope of this review, but several excellent reviews are available (53, 54). In brief, renovascular hypertension may be treated by balloon angioplasty, surgical angioplasty, or nephrectomy. The rate of cure of hypertension by balloon angioplasty (55) is lower with atherosclerotic lesions than with the fibromuscular dysplasia found in the young. This is particularly true of those lesions which occur so frequently at the origin of the renal artery, because the orifice at the aorta may merely dilate without traumatic stretch and return to its usual caliber when the catheter is withdrawn.

Treatment of Hypertension in the Elderly

Nonpharmacologic

In patients with mild hypertension, several nonpharmacologic interventions may be tried in order to reduce the dose of, or even to avoid the use of, antihypertensive medications.

1. **Low Salt Intake.** Moderate reduction in sodium intake has a beneficial effect on hypertension, and patients should be so advised; severe reduction in salt intake is usually not practical.

The data (12) suggesting that high dietary intake of calcium may favorably influence blood pressure have not been confirmed.

2. **Caloric Intake.** The independent effect of obesity on blood pressure remains controversial, but a decrease in body weight in obese patients is beneficial for health in general and should be encouraged.

3. **Hyperlipidemia.** Hyperlipidemia is not causally related to hypertension, but it is an independent risk factor for cardiovascular mortality, and it should be closely followed in hypertensive patients. There is evidence (56, 57) that reduction of serum cholesterol is associated with reduction in cardiovascular mortality. Thus, dietary advice and even pharmacologic intervention should be attempted in hypertensive patients with high lipid levels.

4. **Relaxation Therapy.** Techniques such as biofeedback, yoga, and transcendental meditation have their supporters, but the evidence suggests only a moderate and transient effect on blood pressure (58). Thus, they seldom eliminate the need for drug therapy, though they may help to achieve psychologic well-being.

5. **Exercise Program.** The popularity of aerobic exercise has increased considerably in recent years, and physicians are often questioned about the advisability of a particular exercise program for their patients. A favorable effect on resting blood pressure of aerobic exercises, such as running, walking, or swimming, has not been clearly demonstrated; in fact, during exercise, especially in the untrained subject, systolic blood pressure may increase significantly. However, long-term exercise results in weight reduction, psychologic well-being, increase in plasma levels of HDL cholesterol, and decrease in the increment of work of the heart for any given physical effort (59).

Thus, aerobic exercise can be recommended in patients with mild to moderate hypertension provided there are no other contraindications. In an elderly population, a significant percentage may have some degree of coronary artery disease, and for those patients the prescription for exercise should be carefully and expertly evaluated.

Isometric exercises (60) such as weight lifting should be discouraged because they lead to marked elevations of blood pressure.

Pharmacologic Actions of Antihypertensive Drugs

Currently available antihypertensive drugs are classified by mechanism of action (61) in Table 1; sites of action are indicated in Figs. 1, 2, and 4. Beta blockers (groups 1 and 8 in Table 1) tend to reduce cardiac output.

A number of antihypertensive agents have some negative inotropic effect, through either diminished catecholamine stimulation (beta blockers, guanethidine, guanadrel, reserpine) or inhibition of cellular calcium influx (calcium channel blockers). These agents should be

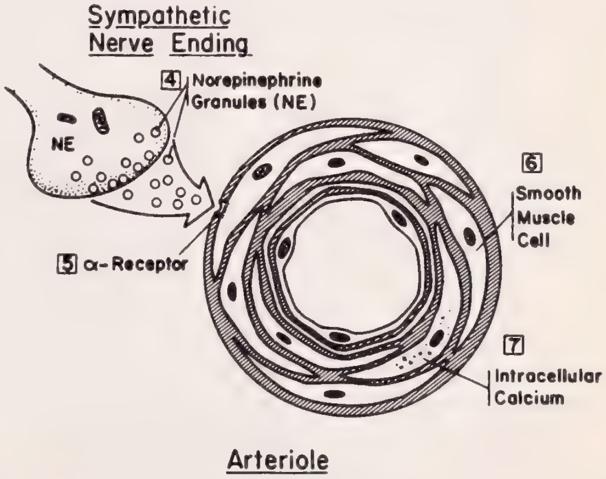


Fig. 4. Sympathetic nerve ending and arteriole. Numbers 4, 5, 6, and 7 refer to drug classes in Table 1.

avoided or used only cautiously in patients in whom heart failure is a present or incipient problem.

Diuretics have the transient effect of lowering the cardiac output. This effect is transient because the autoregulatory mechanism relaxes the arteriolar resistance bed in the face of organ underperfusion, and the reduced total peripheral resistance allows the cardiac output to rise without raising the blood pressure.

Alphamethyldopa, clonidine, and guanabenz (group 2 in Table 1) are central alpha agonists which suppress the outflow of sympathetic impulses and slow the heart by stimulation of the vagus.

The only ganglionic blocking agent (group 3) in use today is trimethaphan, which is infused intravenously for treatment of hypertensive emergencies.

Reserpine, guanethidine, and guanadrel (group 4) affect in varying degrees the uptake, storage, and release of norepinephrine at the sympathetic nerve ending. This relaxes the resistance vessels, and since sympathetic nerves invest the veins, venoconstriction in the orthostatic position may be impeded.

Prazosin (group 5) blocks the attachment of norepinephrine to the alpha receptors on arterioles and veins. Like the group 4 drugs, it may lead to orthostatic hypotension as a side effect.

The vasodilators hydralazine, diazoxide, and minoxidil (group 6) directly impede the contraction of smooth muscle in the arteriolar walls. Nitroprusside relaxes the walls of the veins as well as the arterioles and therefore, unlike the other vasodilators, does not lead to a reflex increase in venous return and cardiac output.

The calcium channel blockers (group 7) as noted above, prevent the cellular uptake of calcium needed for smooth muscle contraction in the walls of blood vessels.

Interference with the function of the renin-angiotensin system (group 8) may be achieved at several levels (Fig. 2): Any of the mechanisms that reduce sympathetic nervous system outflow to the kidney limits the release of renin and hence the production of angiotensin II. Converting-enzyme inhibitors (group 9) not only prevent formation of angiotensin II but also prevent the breakdown of bradykinins, which act as vasodilators. It is possible to block the binding of angiotensin II with saralasin (group 10), but this action is reserved primarily for diagnosis of hypertensive states.

Some of the antihypertensive agents obviously act in more than one site: alpha methyldopa has peripheral as well as central action because it is transformed into alpha methylnorepinephrine and released from nerve endings in place of the true and more potent neurotransmitter norepinephrine. Beta blockers have a central action, possibly at the same site where alpha methyldopa acts, but by blocking stimulatory beta rather than inhibitory alpha effects. Beta blockers also directly inhibit the release of renin, and this action is probably their most important antihypertensive effect. Labetalol (62, 63) is a single molecule in which an alpha blocker has been combined with a beta blocker.

Drug Therapy

The goal of therapy should be to obtain the desidered blood pressure reduction with minimal or no side effect. The approach to treatment should be highly individualized and empirical. The drug chosen should be effective, inexpensive, and have few or no side effects.

There are few areas in medicine where so much disagreement exists as in the setting of criteria for the use of drugs in the elderly hypertensive patient. Most authors would agree that, in the absence of contraindications, systolic pressures equal to or greater than 200 mmHg or diastolic pressures equal or greater than 100 mmHg should be treated, with a view to achieving blood pressures of 160–180/85–95. An interesting suggestion (64) has been offered that MAP be the criterion and that a value greater than 120 mmHg be treated; an MAP of 120 would embrace a range of blood pressures from 190/85 to 140/110. Blood pressure lower than 160/90 might warrant treatment in the presence of unstable angina or congestive heart failure. Some patients with pseudohypertension might be treated with the criteria suggested, and these might be identified as subjects with untoward alterations in hemodynamics with even modest doses of drugs. Occasionally, it may be useful to measure directly the arterial pressure in order to avoid unnecessary and unwise attempts at therapy.

Treatment of hypertension with drugs in the elderly should be undertaken cautiously (65), keeping in mind that these patients are more sensitive than younger patients to a variety of agents because of their lower blood volume, weak baroreceptor response, poor cerebral autoregulation, and tendency to metabolize some drugs more slowly. The elderly should always be warned not to stand up quickly, and when dosages of drugs are increased, the pace should be slow. Thiazide diuretics are often effective in the elderly and usually well tolerated in doses up to 50 mg daily of hydrochlorothiazide with due care for the avoidance of hypokalemia (66). Potassium supplements and potassium-sparing diuretics must be used with great caution in the elderly because they develop hyperkalemia more readily (67). The syndrome of hyporeninemic hypoaldosteronism is common (68, 69), especially in hypertensive diabetics, and in this group hyperkalemia of severe degree is easily provoked. If diuretics are not fully effective, small doses of hydralazine may be added. Reflex sympathetic stimulation is not pronounced in the elderly because of their sluggish baroreceptor response, but the possibility of tachycardia must be borne in mind for patients with coronary artery disease.

Beta blockers are usually not considered a useful first drug in the elderly, but in those with angina they are worth a try. Again, smaller starting doses must be used. There is some advantage to selective beta blockers (70) in patients with pulmonary and peripheral vascular diseases, and possibly drugs with intrinsic sympathomimetic activity (71) in patients with compromised myocardial reserve or sinus node dysfunction.

The role of calcium channel blockers in elderly hypertensives with coronary artery disease, though not clearly established, holds considerable promise. These agents (72) produce not only peripheral vasodilation but also coronary vasodilatation, which maintains the coronary blood flow despite the reduction in blood pressure. In addition, the direct effect on the heart tends to minimize the tachycardia. Side effects may include edema, especially with nifedipine, development of congestive heart failure, and bradycardia.

The peripheral alpha blocker prazosin may be a good alternative. However, occasionally it can produce orthostatic hypotension. One should be particularly aware of what is called "first-dose hypotension," which can be avoided by making sure the patient is not volume depleted and by starting with a dose of 1 mg taken at bedtime.

The centrally acting alpha agonists alphamethyldopa and clonidine may also be used, although they are frequently associated with drowsiness and occasionally with orthostatic hypotension.

Captopril is the only angiotensin-converting enzyme inhibitor available for clinical use in this country. Though captopril is an effective antihypertensive agent, its use has been reserved primarily for treatment of resistant hypertension because of potentially serious side effects. However, several recent studies have shown that captopril, in doses not exceeding 150 mg/day, can be used in mild to moderate hypertension with a very low incidence of toxicity (73).

Drug Interactions

Elderly patients commonly have other diseases besides hypertension, and they may be taking multiple medications. Some of the possible drugs with which interactions may occur include the following:

Sympathomimetic drugs, for bronchospasm (terbutaline, isoetharine, epinephrine, isuprel) or for symptomatic relief of common cold (ephedrine, epinephrine), can produce transient elevations of blood pressure. Some of these compounds may be contained in over-the-counter medications, for example, epinephrine in Primatene.

Phenothiazines, especially chlorpromazine, have a significant peripheral alpha-adrenergic blocking activity and may potentiate the antihypertensive effect of many "regular hypertensive medications." They tend to cause orthostatic hypotension.

Antidepressants that have monoaminooxidase inhibitory effect, such as Parnate (tranylcypromine), Marplan (isocarboxazid), and Nardil (phenelzine), may produce severe hypertension when the patient is exposed to peripherally acting sympathomimetic drugs (nasal decongestants, cold remedies, anti-hay-fever preparations, and asthma medications) or to foods rich in tyramine (aged Cheddar and Camembert cheese and Chianti wines). An additional side effect of these antidepressants is orthostatic hypotension.

Tricyclic antidepressants such as amitriptiline may reduce or prevent the antihypertensive effects of methyldopa, clonidine, guanethidine, and reserpine.

Lithium clearance may be impaired and the risk of toxicity increased by the simultaneous use of diuretics.

Xanthines commonly used for asthma (aminophylline) have some vasodilatory and diuretic action which may potentiate the effects of antihypertensive agents.

Special Groups of Patients

Hypertension in Black Patients. Hypertension in blacks is particularly common and severe. As a group they tend to have low levels of plasma renin and their hypertension may be predominantly volume dependent (74). Diuretics may then be the first line of therapy in this group of patients.

Hypertension with Renal Disease. This group of patients has predominantly volume-related hypertension (75), and they usually require diuretics as part of their therapy. There is evidence that, whatever the etiology of the underlying renal disease, effective control of hypertension can slow the progress of the renal impairment (76).

Severe Hypertension. Persistent hypertension despite the use of two or more drugs represents a therapeutic challenge. The recent availability of potent antihypertensive medicines such as minoxidil (77) has made the treatment of severe hypertension easier. The main disadvantage of minoxidil is the frequent development of hirsutism, which limits its use in women.

Hypertension with Coronary Artery Disease. The combination of these two conditions is rather common (78). This group of patients may benefit particularly from the use of beta blockers and calcium channel blockers.

Hypertension and Diabetes. Diabetes and hypertension are commonly observed together, in part because both conditions are common (79). However, there is some evidence that diabetes predisposes to low-renin (volume-dependent) hypertension (80, 81), which should respond to diuretics. Careful monitoring of serum potassium and glucose levels is required. A second-line drug for diabetics could be prazosin.

Hypertensive Emergencies

The following hypertensive emergencies (82) may occur in elderly patients, just as they may in patients of other age groups: hypertensive encephalopathy, acute aortic dissection, acute left ventricular failure, and acute cerebrovascular accident (Table 2.)

Hypertensive Encephalopathy. Hypertensive encephalopathy is a clinical syndrome characterized by various manifestations of cerebral dysfunction caused by brain edema and cerebral ischemia, which are in turn due to sudden severe hypertension. The condition improves dramatically following reduction of blood pressure. Clinical manifestations include severe and generalized headache, visual complaints, altered mental status (ranging from slight disorientation to coma), nausea and vomiting, papilledema, and transient neurologic deficits.

Hypertensive encephalopathy is diagnosed by exclusion of such entities as stroke, tumor, and uremia. Once the diagnosis seems likely, the patient should be managed with intravenous drugs such as nitroprusside and the blood pressure lowered to near normal levels. Drugs such as clonidine and alphamethyldopa, which can cause

TABLE 2

Drugs for Hypertensive Emergencies in the Elderly

Drug	Route of administration and dose	Onset of action	Duration	Mechanism of action	Indications	Major side effects
Sodium nitroprusside (Nipride)	IV infusion 2.5 μg/kilo/min and titrate	Immediate	1–3 min	Vasodilator	All hypertensive emergencies. Use with a beta-blocker	Nausea, restlessness, methemoglobinemia, thiocyanate accumulation
Diazoxide (Hyperstat)	IV bolus 75 mg and repeat every 5–15 min	Immediate	1–10 hr	Vasodilator	Do not use in dissecting aneurysm or ischemic heart disease	Sodium retention (use with Lasix) hyperglycemia
Trimethophan (Arfonad)	IV infusion 1 mg/min and titrate	Immediate	1–6 min	Ganglionic blocker	All hypertensive emergencies	Urinary retention, ileus
Nifedipine (Procardia)	10 mg sublingually; repeat 10 mg 30 min later if needed	5–15 min	3–5 hr	Calcium channel blocker	All hypertensive emergencies	Facial flushing, headache, burning paresthesia
Labetalol (Normodyne)	20 mg IV over 2 min then 40–80 mg q10 min until BP is controlled or maximal dose of 300 mg is given	5–15 min	Several hours	Both beta and alpha blocker	All hypertensive emergencies	Nausea, faintness

drowsiness and mental confusion, should not be used because the central nervous system side effects of these drugs may make it difficult to assess response to therapy.

Dissecting Aortic Aneurysm Aortic dissection occurs more frequently in men than in women and, particularly in the case of type 3 dissection (83), has its peak incidence about the sixth decade. The patient is usually an elderly man with a history of hypertension who has severe and persistent chest pain. Chest X ray may suggest the diagnosis by showing a mediastinal widening, and an ECG may help to distinguish it from acute myocardial infarction.

When the diagnosis of aortic dissection is made, the blood pressure should be lowered to the lowest possible level that does not interfere with cerebral and renal perfusion. The antihypertensive agent for this purpose should not cause increase in stroke volume or dp/dt. Trimethaphan (Arfonad) would be closest to ideal in this setting because it reduces stroke volume and cardiac contractility and acts rapidly. However, nitroprusside in combination with a beta blocker is more often used because of the familiarity of most physicians with the latter drugs, and because trimethaphan causes rapid onset of side effects due to parasympathetic blockade.

After blood pressure has been normalized and the clinical condition of the patient stabilized, an angiogram should be performed. Proximal dissection is usually treated surgically, but patients with uncomplicated distal dissection can be effectively managed by medical therapy.

Acute Left Ventricular Failure. Acute left ventricular failure in a patient with moderate or severe hypertension is an indication to reduce blood pressure rapidly. It is sometimes difficult to differentiate pulmonary edema secondary to severe hypertension from pulmonary edema that causes reflex hypertension. A history of chronic hypertension, funduscopic findings of severe hypertension, and persistence of hypertension despite routine measures to treat pulmonary edema (oxygen, morphine, furosemide, and so on) would suggest that hypertension is the primary event. Intravenous nitroprusside is the ideal drug in this setting because of its rapid antihypertensive action and the additional venodilatory effect. Very good results have recently been reported with the use of sublingual nifedipine (84).

Acute Cerebrovascular Accident. The management of severe hypertension in the patient with an acute stroke is another area of great debate.

The most obvious indication for lowering blood pressure acutely would seem to be in the case of cerebral hemorrhage, but after decades of study, no data have emerged to prove that patients with cerebral hemorrhage profit from acute antihypertensive therapy. Nevertheless, most physicians feel more comfortable when blood pressure is reduced (85); having made this decision, the physician must observe certain caveats. Blood pressure should be reduced slowly to mildly hypertensive levels, about 160/100, by intravenous agents that have rapid onset and rapid termination of effect and do not alter mental status. If deterioration of the patient's neurologic state follows reduction in blood pressure, it should be allowed to rise. Agents such as nitroprusside, trimethapan, phentolamine, and labetalol are useful, whereas reserpine, methyldopa, and clonidine are contraindicated.

If the clinical picture, CT scan, or lumbar puncture suggests infarction rather than hemorrhage, the advantage of lowering blood pressure is even less obvious than in the case of hemorrhage, and the danger of reducing perfusion in the edematous areas around the infarct may diminish the theoretical advantage of reducing the blood pressure. It might be wise to reduce blood pressure to fairly normal levels in a patient with stroke-in-evolution who is being treated with anticoagulants.

After the acute phase, control of hypertension is safe and may reduce the incidence of new strokes (86). Treatment of hypertension should be undertaken in patients with transient ischemic attacks but should not be considered a substitute for definitive (surgical) therapy where that is indicated.

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Valvular Heart Disease in the Elderly

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Heart murmurs are common in the elderly population, being found in up to 60% of patients (1). This does not mean that they are unimportant (2). The significance of a murmur must be assessed in light of knowledge of the potential benefits of medical versus surgical therapy of the different valve lesions. Symptomatic aortic stenosis, in particular, has a poor prognosis with medical therapy and such a good prognosis with surgical therapy that the approach to the elderly patient with a murmur might be considered a search for and correction of those patients with hemodynamically significant, symptomatic aortic stenosis for whom surgery is feasible. The major overriding concern in this regard is the discrepancy between chronologic and physiologic age. Although it is the most important factor in determining optimal therapy and long-term outcome, unfortunately there are no recognized markers for physiologic age. This is the area in which the art of medicine takes precedence. It is the clinician's estimation of the physiologic age of the patient which guides the therapeutic approach.

Aging and Heart Valves

At the molecular level, the most important aging changes are related to collagen. Although the amount of collagen in the heart increases with increasing age (3, 4), of greater importance is the qualitative change by which collagen becomes increasingly insoluble, chemically stable, and increasingly stiff (5, 6). In addition to being the major component of valves, collagen is interspersed between all myocardial cells and is also a major component of all arteries. Decreased distensibility (increased stiffness) reduces the extent of amplification of the pressure wave while increasing the velocity of the pulse wave in the major arteries (7).

With aging, the fibrous stroma of the valves shows a decrease in the number of nuclei (8, 9). At the sites of maximum cusp movement there is collagen degeneration, lipid accumulation, and calcification. Microscopically identifiable calcification will be found in at least one valve in about one-third of patients over 70 years of age (8), more commonly in the aortic than the mitral valve. Nodular thickening on the atrial surface of the mitral leaftlets appears to be age-related, whereas the incidence of nodules on the aortic cusps does not increase after middle age. Tricuspid and pulmonary valves are rarely involved. Mucoid degeneration of the mitral leaflets is pathologically identical to the myxomatous change described in younger patients and may produce the clinical syndrome of mitral valve prolapse. Myxomatous change has been attributed to a variety of etiologies, and age-associated degeneration may be one cause of this abnormality. In other patients, this may represent a clinically unimportant abnormality that has been present for some years. Calcification of the mitral annulus, although not universally present in the elderly, is found with increasing frequency with age and is generally considered to be an exaggeration of normal aging changes. In about 10% of autopsies of persons over 50 years of age, some calcification of the mitral annulus will be found, varying from small spicules to solid calcification of the entire ring (8).

These age-associated changes in heart valves may progress to hemodynamically important valve lesions. Calcific degeneration of the aortic valve is the most common cause of aortic stenosis in the elderly (8). Heavily calcified mitral rings have been associated with obstruction, incompetence, heart block, and endocarditis.

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Assessment of the Elderly Patient with Valve Disease

Generally speaking, the history in the elderly patient is approached in the same manner as in a younger patient. In the elderly patient with a long history of numerous diseases, the chronology may be more difficult to clarify. The importance of the drug history cannot be overemphasized. Often specific cardiovascular symptoms will be absent or overshadowed by nonspecific complaints or symptoms related to other systems. In addition to assessing the symptomatology attributable to the cardiovascular system, it is especially important in elderly patients to determine general health and overall functional capacity and to what extent the cardiovascular illness affects these two. These considerations form the basis of many of the therapeutic decisions that have to be made in regard to the cardiac disease. The presence of other illnesses is also of importance in terms of their interaction with the cardiovascular system.

The approach to physical examination is the same as with younger patients and should include the effects of postural changes and other maneuvers. The general physical examination is extremely important because of the frequent occurrence of other diseases. The effect of altered distensibility on the characteristics of the pulses has been alluded to above. Rigidity and tortuosity of the peripheral arteries have no clinical significance but may produce bruits not related to functionally important abnormalities (9, 10). When the involved arteries are close to the heart, these bruits may be interpreted as murmurs.

The loss of subcutaneous fat may make the jugular venous pulse easier to see, but kinking of the external jugular veins at the junction with the subclavian makes these veins unreliable for assessing venous pressure. Furthermore, compression of the central veins by the unfolded aortic arch may falsely elevate pressure in the internal jugular vein. Thus, care must be exercised to be certain that pulsations are visible when determining venous pressure. Deep inspiration will usually reduce the compression, allowing the column of blood to drop to the appropriate level (11). The characteristics of the waveform have the same implications as in younger patients.

Skeletal deformities make the localization of the apical impulse more difficult and less meaningful, but the quality of the impulse, when felt, carries the same diagnostic weight as in younger patients. Heart sounds are generally less intense but the significance of their intensity relative to one another remains the same. The splitting of the second heart sound is usually narrower in the elderly (12). Abnormalities of splitting have the same diagnostic implications. Fourth heart sounds may be normal in the elderly, whereas third heart sounds are always abnormal—the opposite of the situation in young adults (13). The majority of elderly patients have systolic ejection murmurs not associated with significant valvular disease and attributed to aortic sclerosis (1, 2). The valvular abnormalities underlying murmurs other than the ejection murmur are the same as in younger patients.

The most common causes of heart failure in the elderly are ischemic heart disease and hypertensive heart disease. Valvular disease is less common. In the elderly, the diagnosis of congestive heart failure is more likely to be complicated by the presence of other diseases. The coexistence of chronic pulmonary disease makes assessment of effort dyspnea, the dominant symptom of congestive failure, extremely difficult. The presence of ankle edema does not necessarily imply the presence of congestive heart failure, and local causes must be excluded. It should not be attributed to congestive heart failure in the absence of other signs of failure, for example, gallops, elevated jugular venous pressure, or hepatomegaly.

"Normal" Values. All the investigations that one would apply to younger patients are applicable to the elderly, but the range of normal variation may be different. Particularly in the case of the noninvasive cardiologic investigations, normal values for the elderly have not been well defined. Electrocardiographic changes are common in the elderly (14). The QRS axis gradually moves leftward (15–17), but values less than −45° are definitely abnormal though not necessarily indicative of underlying heart disease (14, 17). Limb lead voltages decrease with advancing age (15). Precordial voltage changes are less consistent, and increases may not necessarily indicate hypertrophy (18).

Some degree of left ventricular hypertrophy is a normal concomitant of aging, and this is reflected in increased echocardiographic left ventricular wall thickness (19–21), but the changes in other echocardiographic parameters are less well defined. Although attempts have been made to determine the normal echocardiographic values for elderly patients (21), no values have as yet been generally accepted. However, the qualitative features of the echocardiogram are as reliable as in younger patients (22), and grossly abnormal dimensions are quite clearly abnormal.

Initially, it was thought that the response to exercise radionuclide angiography was markedly different in normal elderly patients in that ejection fraction often decreased with exercise and the development of regional wall abnormalities was common (23, 24). However, a more recent study suggests that the same criteria for interpreting nuclear angiography are applicable regardless of age (25).

Aortic Valve Disease

Overall, calcification of a congenitally bicuspid valve is the most common cause of aortic stenosis, but the frequency of this pathologic finding decreases with increasing age. Isolated aortic stenosis after age 75 is almost always a result of degenerative calcification of a normal valve (8, 26). In about one-half of the elderly patients with aortic stenosis, associated aortic incompetence can be demonstrated (9). Aortic stenosis combined with mitral valve disease is usually rheumatic in etiology.

Modes of Diagnosing Aortic Stenosis. The major clinical manifestations of aortic stenosis remain angina, congestive heart failure, and syncope. Systolic ejection murmurs are frequently found in elderly patients. The distinction between aortic sclerosis and aortic stenosis can often not be made on clinical grounds. In fact, one can argue that the two processes are basically the same and that the only true distinction between them is the presence or absence of a gradient across the aortic valve. The decrease in arterial elasticity that accompanies aging will mask the otherwise slow upstroke of the pulse wave in aortic stenosis. The heart sounds are generally reduced in intensity in elderly patients, and thus, the reduction and the intensity of the aortic component that accompanies aortic stenosis may be difficult to appreciate. The murmur of hemodynamically significant stenosis is generally louder and longer than that in the absence of a gradient and tends to peak later in systole (27, 28).

Although left ventricular hypertrophy may not be apparent on physical examination, in the presence of significant aortic stenosis, ECG and echocardiographic evidence of hypertrophy will usually be present. As other causes of hypertrophy can coexist with aortic sclerosis, the combination of murmur and hypertrophy is not diagnostic. However, the absence of any evidence of left ventricular hypertrophy makes hemodynamically significant stenosis unlikely. Echocardiography can demonstrate the thickening of the aortic cusps, but attempts to determine the orifice area have been hampered by the amount of calcification that is usually present. The extent of calcification as seen on chest X ray is thought to correlate with the severity of the stenosis (29).

The fact that surgical treatment of symptomatic aortic stenosis is low in risk and offers potential benefits emphasizes the importance of not overlooking this diagnosis. The need for cardiac catheterization prior to aortic valve replacement remains somewhat controversial (30, 31), but current noninvasive tests cannot be relied upon to determine the severity of stenosis in the elderly patient with valvular calcification. Doppler ultrasound may overcome many of these problems and allow a definitive diagnosis to be established (Fig.) Unfortunately, suitable Doppler signals appear to be more difficult to obtain in the elderly, and the correlation with the measured gradient may be less reliable (32). Although, statistically, patients who do not complain of angina are unlikely to have associated obstructive coronary disease, only coronary angiography can determine this with certainty. In our experience, as in others', failure to correct significant coronary disease compromises the long-term results of aortic valve replacement, even in elderly patients (33, 34). Furthermore, in our laboratory, cardiac catheterization complications have been related primarily to left ventricular angiography. Therefore, unless we suspect the presence of associated mitral insufficiency, we do not perform contrast angiography at the time of catheterization but perform radionuclide angiography separately. Although the elderly patient with severe aortic stenosis represents a relatively high risk patient for cardiac catheterization (35), this procedure must be offered to any suitable patient in whom the diagnosis cannot be otherwise excluded.

Aortic Incompetence. The most common valve lesion found in the elderly is aortic incompetence (9). It occurs as an isolated lesion, in over 50% of patients with aortic stenosis and in about 40% of patients with rheumatic mitral disease. Degenerative dilatation of the aortic root, calcific degeneration of the aortic valve, and rheumatic heart disease are the most common causes. Syphilitic aortitis, once a very important cause, is still seen in the elderly population but with decreasing frequency. All the recognized causes of aortic incompetence in younger patients may be seen in older patients, but most are relatively rare.

Aortic incompetence in the elderly is similar in its presentation and clinical features to aortic incompetence in the young. The clinical diagnosis poses no particular problems in the aged. Its presence can often be confirmed by noninvasive means, which may also provide evidence for its etiology. Except when sudden in onset, aortic incompetence is well tolerated hemodynamically, and thus surgery in elderly patients should only be considered for those patients whose symptoms cannot be controlled medically.

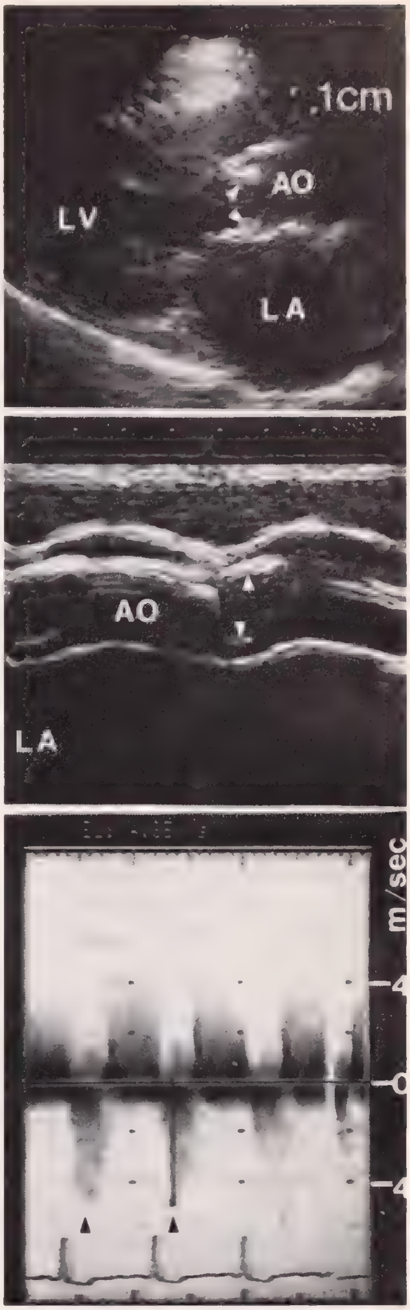

FIG. Combined echocardiographic study. *LV, left ventricle, Ao, aorta, LA, left atrium. Illustration courtesy of Dr. C. Pollick* **Upper panel,** 2D echo, parasternal long axis. Arrows point to aortic valve leaflets, which appear to open well, although there is "doming" of tips. **Middle panel,** M-mode echo. Arrows point to virtually normal separation of thickened leaflets in systole. **Lower panel,** Continuous-wave Doppler, aimed from apex through aorta. Arrows point to peak aortic velocity (4.85 m/s) which suggest an aortic gradient of 95 mmHg (gradient at catheterization was 90 mmHg).

Mitral Valve Disease

Mitral incompetence may be secondary to left ventricular enlargement of any etiology. Papillary muscle dysfunction and mitral valve prolapse are also recognized causes of mitral insufficiency in the elderly population (36). Rheumatic mitral valve disease has an estimated prevalence of 2%–3% in the elderly population (9). Stenosis dominates in one-third of these patients; incompetence dominates in the remainder. Calcification of the mitral annulus occasionally presents as mitral stenosis, as does the rare left atrial myxoma (37).

The clinical presentation of mitral valve disease in elderly patients is generally similar to that in younger patients. Angina is more common, occurring in about 10% of patients (9). In the majority of these cases, coronary artery disease is also present.

The features of the physical examination carry the same implications as in younger patients. Because of the extent of valvular calcification, the increased intensity of the first heart sound and the opening snap may both be absent.

In the elderly patient with mitral stenosis, the electrocardiographic features of right ventricular hypertrophy are uncommon, but the characteristics of left atrial enlargement may be seen if sinus rhythm is still present. Electrocardiographic evidence of left ventricular hypertrophy will be seen in the presence of moderate mitral incompetence. Echocardiography has proven reliable, not only in the diagnosis of mitral stenosis, but often in the assessment of its severity. It is also a useful technique in the diagnosis of mitral valve prolapse but is of limited usefulness in other cases of mitral incompetence. The extent of mitral valve calcification as seen on chest X ray correlates with the gradient in mitral stenosis (38).

Mitral valve disease not associated with atrial fibrillation or congestive failure appears to have no significant effect on the life expectancy of elderly patients (28). Since mitral valve replacement has generally been considered a less satisfactory operation than aortic valve replacement, surgery is generally reserved for patients whose symptoms cannot be controlled by medical means, including attempts to maintain sinus rhythm, control of ventricular response rate in atrial fibrillation, and treatment of congestive heart failure. However, as a result of these considerations, mitral valve surgery is often delayed longer than aortic valve surgery. This may account for some of the lack of benefit from mitral valve replacement.

Valve Surgery

Many reports have appeared concerning the results of valve replacement surgery in the elderly

(33, 39–43). Reviewing this literature is complicated by the fact that there is no clearly defined line of demarcation between the elderly population and the population as a whole. Various authors have used ages ranging from 50 to 80, depending on the nature of the surgery and the period during which it was performed (33, 39–44).

In addition, both medical and surgical therapy have changed dramatically over the past decade, and much of the information published just five years ago is of questionable validity today. Current results are far superior to earlier experience, particularly in respect to older patients. For isolated aortic valve replacement, with or without coronary bypass grafting, one anticipates an operative mortality that is almost neglible, a 90% 3-year survival, and greater than 80% of patients functionally improved. Isolated mitral valve replacement still carries a 4%–10% mortality and a 3-year survival of only 66%. However, 90% of survivors are clinically improved. Some complex procedures, for example double valve replacement, continue to be associated with a high operative mortality that may not be clinically justifiable, whereas the successfulness of others has been remarkable (Table).

Infective Endocarditis

Infective endocarditis is a diagnosis that is commonly overlooked in the elderly because of the misconception that it is usually a disease of young and middle-aged patients. In fact, the clinical spectrum has shifted toward older age groups, and the majority of patients in the more recent series have been 60 years of age and older (45). The typical symptoms of malaise, weakness, anorexia, and weight loss occur in less than one-third of patients, and even these symptoms tend to be modified in the aged. Psychiatric disturbances, persistent back pain, or embolic episodes are common initial symptoms (46–48); progressive renal insufficiency (49) or metastatic abscess are less common. The presence of other pathologic processes further obscures the diagnosis.

As in younger patients, one-third have no underlying heart disease. Although rheumatic valvular disease remains an important etiology (50), nonrheumatic cardiac abnormalities, particularly involving the aortic valve, are increasingly important in the elderly (9, 51, 52).

The combination of fever and heart murmur is the most obvious clue to the diagnosis, but both may be absent. High fevers are uncommon, and low-grade fevers are likely to be overlooked because basal body temperature in the elderly is generally lower (53). The murmurs are usually soft and not readily distinguishable from those commonly found in healthy older patients. Atrial fibrillation is not uncommon and is not evidence against the diagnosis (47). The classic peripheral manifestations are rarely seen.

Echocardiography has proven useful in the diagnosis and monitoring of patients with endocarditis (54, 55). Blood cultures remain the basis of diagnosis and treatment.

Treatment is essentially the same as in younger patients and consists of a minimum of 4 weeks of intravenous antibiotics chosen on the basis of blood culture results.

Infective endocarditis in the elderly is associated with 30% mortality, approximately twice that in younger patients (47). The delay in diagnosis does not appear to account for all of this excess mortality. Surgical intervention is indicated for medically refractory failure or persistent infection despite adequate antibiotic therapy. Although surgery is associated with an extremely high risk, medically refractory congestive heart failure in this situation is associated with 90% mortality, and persistent infection is universally fatal (56).

TABLE

*Results of Valve Surgery in Patients Aged 70 and Older 1979–1984**

	No. of pts	Age		Combined with ACB	Deaths		Follow-up (yr)	
		Mean	(Range)		Early	Late	Mean	(Range)
Single valve								
Aortic	41	73.4	(70–83)	28	0	1	2.6	(1–6)
Mitral	23	73.7	(70–77)	19	1	1	3.7	(1–5)
Double valve	8	75.4	(71–81)	—	2	1	2.0	(1–4)
Aortic valve + aortic root replacement	7	72.7	(70–76)	—	0	0	2.1	(1–3)

ACB, aortic coronary bypass.

* David TE, Berman ND. Unpublished observations.

Antibiotic prophylaxis is warranted in elderly patients with known hemodynamically significant valvular disease. However, murmurs are common in elderly patients and have no hemodynamic significance in most situations. The use of prophylaxis in these patients is controversial. In general, the consequences of endocarditis are so devastating that prophylaxis should probably be given to any patient who may have a structural abnormality underlying a murmur.

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Cardiac Arrhythmias in the Elderly: Selected Aspects

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This article considers selected topics dealing with the pathogenesis, recognition, and management of cardiac arrhythmias in the aged. Disorders of impulse formation and transmission increase with age and are common in the elderly. Although good epidemiologic data on prevalence are not available, and there is no precise definition of "elderly," a recent study by Fisch (1) indicates the order of magnitude of the problem. In this survey of 2,500 subjects over the age of 65, electrocardiographic abnormalities were present in 57%. About 80% of the electrocardiographic abnormalities were disorders of impulse formation or transmission. Fifty percent of the patients had abnormal left-axis deviation, 10% atrial premature beats, 6% ventricular premature beats, 9% first-degree atrioventricular block, 8% atrial fibrillation, 5% right bundle branch block, and 3% left bundle branch block. Other studies, including ambulatory electrocardiography, also reported a high prevalence of cardiac arrhythmias (2, 3).

Pathogenesis

The aging process itself is associated with a series of anatomic, physiologic, and metabolic changes that may, in part, account for the frequency of arrhythmias in the aged and that certainly modify the clinical and therapeutic responses of elderly subjects to arrhythmias (Table 1).

Anatomic Changes. Several diseases occur frequently in the aging heart (4): coronary atherosclerosis in at least 50%; amyloid deposits (sometimes heavy) in 40%; calcification of the mitral annulus in 10%; myxomatous disease of the myocardium and valves in a substantial number. All of these may be causally related to arrhythmias. Of particular importance is the occurrence of patchy fibrosis throughout the myocardium. In part, this is due to atherosclerotic disease, but, in addition, it occurs in the absence of atherosclerosis, the sclerodegenerative diseases of Lenegre (5) and Lev (6). The conduction system is especially vulnerable, and the frequent occurrence of left anterior fascicular block, other intraventricular conduction abnormalities, and ultimately advanced atrioventricular block is probably the result of these patchy areas of fibrosis.

A qualitative change in myocardial collagen has been noted in the aging heart. The collagen becomes increasingly insoluble and stiff (7). These changes may affect ventricular distensibility and contractility and, indirectly, impulse formation and transmission. Myocardial deposition of lipid substances is also common, but the relationship of this to cardiac function is unclear. Age-related anatomic changes in the conduction system are more specifically related to arrhythmias. Reference has already been made to fibrosis in the His-Purkinje system. In addition, there may be loss of myofibers and an increase in elastic tissue in the distal His bundle. The number of pacemaker cells in the sinoatrial node decreases with age, and after the age of 75, the node contains less than 10% of the normal number of such cells (8). This may, in part, account for the prevalence of the group of arrhythmias which make up the sick sinus node syndrome. The atrioventricular node does not appear to change as it ages.

Electrophysiologic Changes. Paralleling these anatomic changes are important electrophysiologic alterations. The action potential amplitude and the rate of depolarization in the transmem-

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TABLE

Factors Predisposing to Cardiac Arrhythmias in the Aged

Anatomic
Specific diseases: atherosclerosis, calcification of mitral annulus, amyloid disease, myxomatous degeneration
Myocardial fibrosis (secondary or idiopathic)
Loss of P cells in S-A node
Loss of myocardial fibers and increase in elastic tissue in bundle of His

Metabolic
Collagen dysplasia
Fatty infiltration

Physiologic
Reduced conduction velocity; decreased dv/dt of phase 0
Decreased resting potential
Decreased responsiveness of B receptors

Other
Pulmonary disease
Reduced renal function

brane action potential are decreased in aging myocardial cells of the rat and dog (9, 10). Repolarization abnormalities involving phases 1 and 2 of the action potential have also been observed. Ischemic disease, myocardial fiber stretch, cardiac enlargement, and other pathologic processes in the aging heart also alter the electrophysiologic properties of myocardial cells (11). The net effect of these changes may be to enhance automaticity and induce local areas of block.

Age-related changes in the automatic nervous system have also been identified. Phasic or respiratory sinus arrhythmia is attenuated (12), and there is a decrease in the magnitude of the blood pressure responses to the Valsalva maneuver (13). Beta-adrenergic receptors are less responsive to both agonist and antagonist drugs. Recent studies suggest a reduced affinity of the leukocyte receptors of older subjects for β agonists (14).

The net effects of these anatomic and physiologic changes in the aging heart provide a basis for the frequent occurrence of arrhythmias in elderly subjects. They are consonant with current theory that disorders of impulse formation are caused by micro- or macroreentry circuits, by enhanced or abnormal automaticity, or by triggered rhythms due to after-depolarization, and that abnormalities of impulse transmission are the result of areas of slowed or absent conduction.

Finally, noncardiac diseases in the elderly may predispose to spontaneous or drug-induced arrhythmias, particularly pulmonary ventilatory insufficiency and renal excretory insufficiency.

It is apparent that the electrogenesis of cardiac arrhythmias in the aged is not significantly different from that in younger persons. Two aspects of this subject will be discussed here. Both deal with the nosology of ectopic rhythms and hence are of considerable practical importance. The current classifications of ectopic rhythms in general, and paroxysmal supraventricular tachycardia in particular, are based on clinical and experimental methods developed during the past 15 years. The introduction of His bundle electrocardiography by Scherlag and his associates about 15 years ago (15) ushered in the modern era of intracardiac electrophysiology. The initial technique was quickly modified to include methods for recording multiple electrograms from many intracardiac sites, thus permitting the precise determination of the sequences of intraatrial, atrioventricular, ventriculoatrial, and intraventricular excitation. Data from such studies have, on the one hand, confirmed many important electrophysiologic concepts which in the past had been purely deductive constructs from clinical electrocardiograms—mechanisms such as concealed conduction, aberrant ventricular conduction, and reentry. On the other hand, these studies also demonstrated the frequent inaccuracy of standard electrocardiographic criteria for the recognition of certain cardiac arrhythmias (16)—the differentiation of ventricular from supraventricular tachycardia, the differentiation of aberrant ventricular conduction from ventricular ectopy, and the separation of the different forms of supraventricular tachycardia. In addition, these techniques permitted electrophysiologic analysis never before possible—the precise location of reentrant pathways, the precise location of atrioventricular conduction delays, and the applications to pharmacologic and surgical therapy.

While it is not possible here to review these concepts in detail, one of them will be discussed because it represents an important idea in the taxonomy of ectopic rhythms. Based on electrophysiologic investigations in humans and on isolated cardiac tissue, it is now possible to classify all ectopic rhythms into three main categories: those due to reentry; those due to manifest automaticity of subsidiary pacemakers; and those due to after-depolarizations (triggered rhythms).

Reentry. The phenomenon of reentry had been postulated by early workers in clinical and experimental electrocardiography (17). However, despite its experimental demonstration by Schmitt and Erlanger (18), it remained a theoretical concept in relation to human arrhythmias until its validity was confirmed by intracardiac electrophysiologic studies (16).

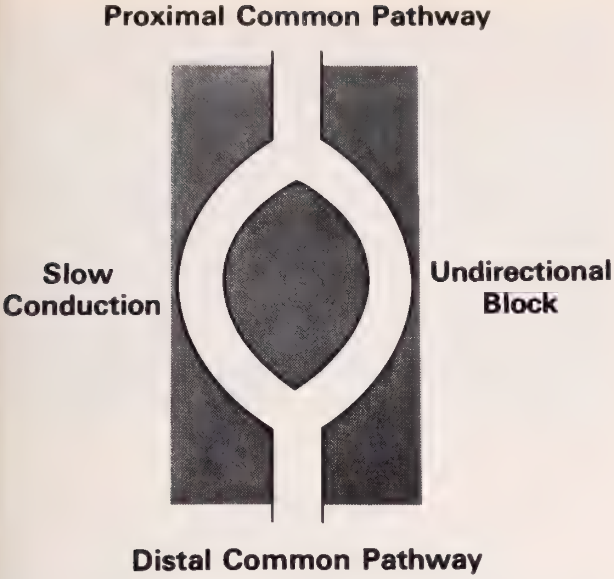


Fig. 1. Schematic representation of reentry system.

The mechanism of reentry may be described with the aid of an oversimplified diagram (Fig. 1). Four elements must be present to form the reentry circuit: a proximal common pathway; two or more subdivisions of this pathway; a common distal pathway; and different refractory periods and conduction velocities in the branches of the proximal pathway. One of these branches must have unidirectional block, the other slow conduction. When these conditions are satisfied, an impulse in the proximal common pathway will not be conducted in the branch with unidirectional block and will preferentially enter the other branch with slow conduction. When the impulse reaches the distal common pathway, it can enter the blocked pathway in retrograde manner and reenter the proximal common pathway, thus completing the circuit.

If enough time has elapsed and the reentry pathway is not too short, the slow-conduction branch pathway can accept the impulse a second time, and the circuit may be completed as before. The reentry circuit may be located anywhere in the heart, resulting in various forms of premature beats or paroxysmal tachycardia. As long as these conditions persist, the circus movement will continue. If the reentrant pathway becomes refractory to the approaching wave of depolarization, or if unidirectional block is no longer present, reentry will cease. Thus, initiation or termination of reentry can be effected by changes in refractory periods or conduction velocity or by properly timed premature depolarizations of atria or ventricles.

Automaticity. Automatic rhythms have, of course, been recognized for decades (17), and the physiologic basis of automaticity was demonstrated when recording of the transmembrane action potential of single cells became possible. Spontaneous phase-4 depolarization was identified as the hallmark of pacemaker cells located throughout the specialized myocardium. Electrical chaos in the heart was prevented by passive depolarization of the potential secondary sites of impulse formation by signals arising from faster sinus node. As a consequence, the two mechanisms whereby latent pacemakers could produce manifest arrhythmias were identified.

The first of these mechanisms is a change in the rate relationship between the sinus node and subsidiary pacemakers such that the rate of a lower pacemaker exceeds the rate of the sinus node. This may occur if the sinus node decelerates below the unchanged rate of a secondary pacemaker, or if a lower pacemaker accelerates above the unchanged rate of the sinus node.

The second mechanism consists of higher degrees of atrioventricular block which, in effect, reduce the rate of excitation of the ventricles by the sinus node and may reduce it below the inherent rate of a lower pacemaker in the atrioventricular junction or more distal His-Purkinje system. Automatic rhythms are, in a sense, "normal" manifestations of automaticity, since they originate in cells that normally possess the capacity for spontaneous impulse formation. However, under certain circumstances, particularly ischemic injury, myocardial cells may become partially depolarized, resulting in an increased rate of impulse formation. This has been referred to as abnormal automaticity, a mechanism that may be an important cause of some ectopic ventricular rhythms that follow experimental myocardial infarction.

After-Depolarization. The third general mechanism thought to be responsible for ectopic rhythms is based on experimental observations made by Paul Cranefield (19). He demonstrated the presence of after-depolarizations occuring either during phase 3 of the transmembrane action potential or later, during phase 4. Such afterpotentials could be provoked or modified by a variety of physiologic or pharmacologic interventions. Although many of the after-depolarizations failed to reach threshold, those which did could initiate single or successive propagated impulses referred to as "triggered" rhythms. The relevance of these observations to clinical cardiac arrhythmias is not entirely clear, but they may be the basis for a variety of ectopic supraventricular and ventricular rhythms.

The Supraventricular Tachycardias. In addition to permitting a comprehensive and more rational understanding and classification of ectopic rhythms in general, electrophysiologic studies have in particular clarified a long-standing area of ambiguity, the classification of the supraventricular tachycardias. In the past it was believed that regular supraventricular tachycardias could be classified into two groups, those arising in the atria ("paroxysmal atrial tachycardia") and those arising in the atrioventricular node ("paroxysmal A-V nodal tachycardia"). Early workers believed these arrhythmias involved a circus movement mechanism, but later, especially as a result of the work of Scherf and Schott (20), they were thought to result from a rapidly discharging single focus in the atria or atrioventricular node.

Modern electrophysiologic studies have shown the original theory to be correct for the most part. It is now known that the rubric "paroxysmal supraventricular tachycardia" includes at least five different arrhythmias, all but one of which have reentry as their basis. Precise identification of the various forms of paroxysmal supraventricular tachycardia can be made only with the aid of electrophysiologic study. The electrocardiographic distinctions described below are helpful but not absolutely specific.

Reentrant Atrioventricular Nodal Tachycardia. The most common of these arrhythmias is reentrant A-V nodal tachycardia. It may be suspected when the electrocardiogram displays a regular supraventricular rhythm with a rate range of 150–200 and no visible P waves because the atria and ventricles are excited almost simultaneously and the retrograde P wave and QRS complex are superimposed.

Reentrant Atrial Tachycardia. Reentrant atrial tachycardia usually causes visible P waves and a shorter P-R than R-P interval. The rate is slower than for reentrant A-V nodal tachycardia, and the P waves are distinctly different from the sinus P waves. This arrhythmia begins and ends abruptly (as do all the reentrant tachycardias), usually lasts for only brief periods, and is commonly seen in Holter recordings.

Reentrant Sinus Tachycardia. Reentrant sinus tachycardia is similar to reentrant atrial tachycardia, except that the P wave morphology is similar to the sinus P wave.

A-V Bypass Tract Tachycardia. Atrioventricular bypass tract tachycardias are the result of conduction through one of the many A-V bypass tracts. The common form of this arrhythmia involves retrograde conduction through the bypass tract and causes a rapid, regular supraventricular tachycardia in which the retrograde P wave just follows the QRS complex.

Automatic Atrial Tachycardia. The only arrhythmia in this group not due to reentry is automatic atrial tachycardia. The rate tends to be relatively slow, 120–150; the P wave differs in form from the sinus P wave and precedes the QRS complex. Type I second-degree A-V block is usually present. This arrhythmia is commonly referred to as paroxysmal atrial tachycardia with block.

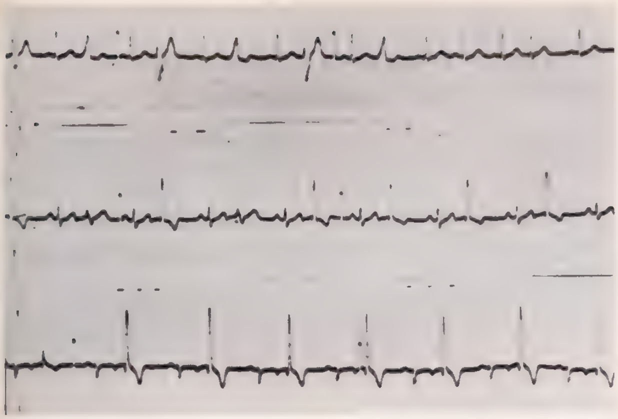
Recognition: Six Common Problems

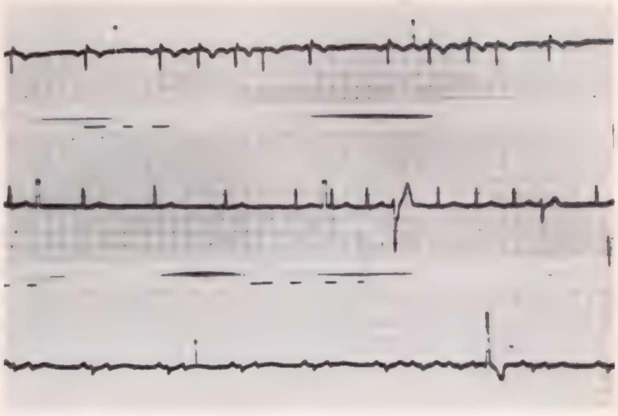
Six common arrhythmias that may cause difficulties or confusion in interpretation are discussed here.

Atrial Premature Beats. Atrial premature beats are not only very common, but they are often erroneously diagnosed as A-V junctional premature beats, ventricular premature beats, sinus arrest, or sinoatrial exit block. The reasons for these errors are (a) the premature P wave that defines the atrial premature beat is often superimposed on the preceding T wave, and the distortion of the T wave may be overlooked; (b) atrial premature beats are often nonconducted or blocked causing sudden lengthening of the R-R interval; and (c) atrial premature beats are frequently associated with aberrant ventricular conduction simulating ventricular premature beats.

All these variants may occur in the same electrocardiogram resembling a complex arrhythmia (Figs. 2–4). Simple identification of the premature P wave should avoid these diagnostic pitfalls.

Atrial Fibrillation and Flutter. Atrial fibrillation and atrial flutter are sometimes difficult to differentiate. Fibrillation deflections may be large and have a constant cycle length for brief periods resembling flutter waves, and flutter waves are sometimes low in voltage, as is usually true for fibrillation deflections. Flutter waves are absolutely homogeneous in morphology and cycle length, and in inferior leads 2, 3, and aVf there are no isoelectric intervals separating adjacent deflections. Fibrillation deflections are heterogeneous in morphology and cycle length. If these distinctions are enforced, the differentiation between flutter and fibrillation should almost always be easy (Figs. 5, 6).





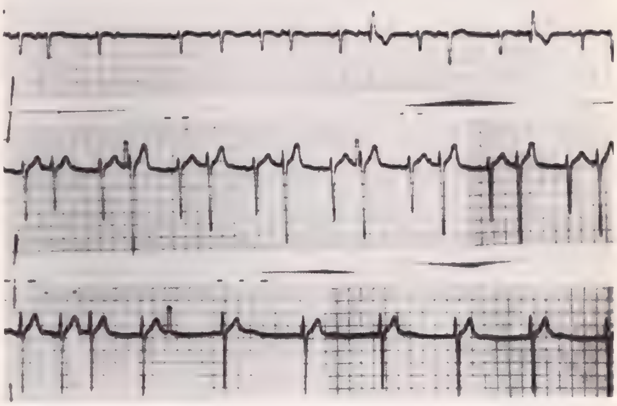


Fig. 2. Above left Standard leads 1, 2, 3. Atria in sinus rhythm. Multiple atrial premature beats occur in bigeminy, distorting terminal portion of sinus T waves. Aberrant ventricular conduction simulates ventricular premature beats.

Fig. 3. Above right Same patient. Leads aVr, aVl, and aVf. Multiple nonconducted atrial premature beats in bigeminy.

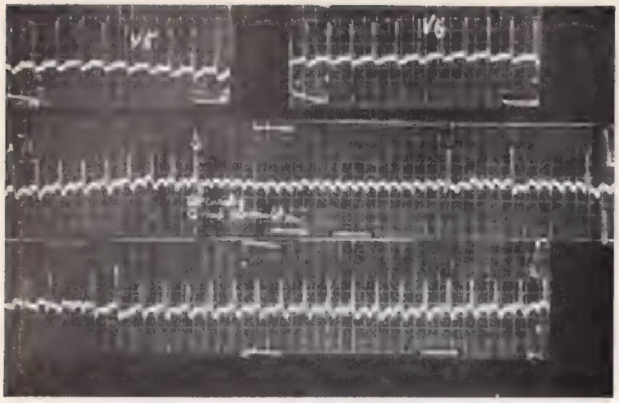
Fig. 4. Right Same patient. Precordial leads V_1, V_2, and V_3. Multiple atrial premature beats in bigeminy, some nonconducted, some conducted with aberrant ventricular conduction.

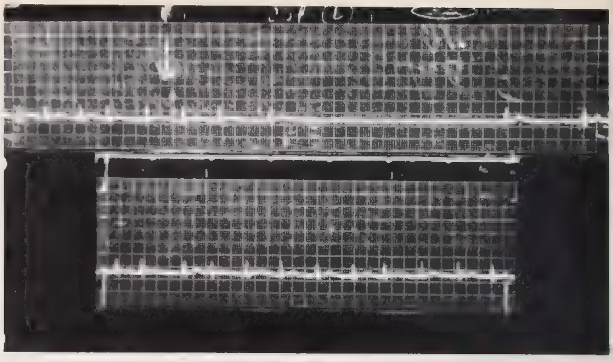
The term "flutter-fibrillation" is commonly used when the atrial deflections are typical of fibrillation but intermittently become larger and more regular. In my opinion this term is a misnomer. Most electrocardiograms of this type are examples only of atrial fibrillation. The term should probably be reserved for the specific arrhythmia in which one atrium is fibrillating and the other is in flutter. This diagnosis can be made only by simultaneously recording electrograms from the right atrium (using an intracardiac electrode) and the left atrium (using an esophageal or coronary sinus probe).

Since atrial fibrillation is one of the common tachycardias in patients with ventricular preexcitation, and since many of the cases of fatal ventricular fibrillation in preexcitation have been preceded by atrial fibrillation, an observation first reported by Sellers et al (21) is important: some patients with ventricular preexcitation and atrial fibrillation have, intermittently, very short R-R intervals, equal to or less than 0.2 sec. It is these patients who are likely to have very rapid average ventricular rates, often the predecessor of ventricular fibrillation. Therefore, very short R-R intervals in atrial fibrillation may be a marker for ventricular preexcitation. In these patients it is probably prudent to omit the use of digitalis, since the glycosides may shorten the refractory period of the bypass tract and paradoxically increase the ventricular rate.

A still unresolved problem in atrial fibrillation is the differentiation of ventricular ectopy from aberrant ventricular conduction of supraventricular impulses. The clinical importance of aberrant ventricular conduction in atrial fibrillation was emphasized by Gouaux and Ashman many years ago (22) when they reported that aberrant beats may occur in succession, simulating ventricular tachycardia (Fig. 7). Atrial fibrillation predisposes to aberration because of the irregular ventricular rhythm. Since there is a direct relationship between cycle length and refractory period duration in the His-Purkinje system, when a short cycle is preceded by a long one, the beat terminating the short cycle may reach the distal conduction system when part of it is still refractory. This impulse will necessarily activate the ventricles differently from normal, and the QRS morphology will be different or aberrant. However, true ventricular premature beats may be initiated in the same way.

Clinical electrocardiographers have considered several ways that aberrant beats and true pre-





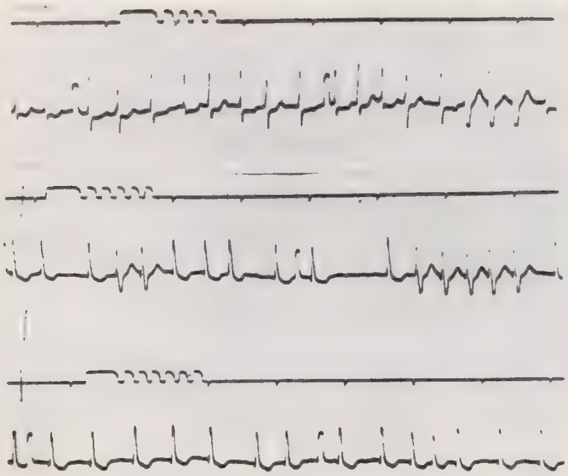


Fig. 5. Above left Atrial flutter with 2-to-1 atrioventricular conduction. Vagal stimulation causes complete atrioventricular block and suppresses subsidiary pacemakers. Flutter deflections are absolutely homogeneous in cycle length and morphology.

Fig. 6. Above right Atrial fibrillation. Vagal stimulation causes marked slowing of ventricular rate displaying fibrillation deflections low in voltage and heterogeneous in cycle length and morphology.

Fig. 7. Left Atrial fibrillation. Leads V_4, V_5, and V_6. Short runs of aberrant ventricular beats displaying delayed excitation of right ventricle are initiated when short R-R interval is preceded by abrupt lengthening of R-R cycle. While aberrant ventricular conduction of supraventricular impulses is the suggested mechanism, ectopic nonsustained ventricular tachycardia cannot be excluded with certainty.

mature beats may be differentiated. Aberrant ventricular conduction is more likely to be caused by delayed conduction in the right bundle branch system than the left, and aberrant beats usually show right bundle branch block configuration. This is not pathognomonic of aberration, since ectopic beats may arise in the left ventricle and cause a right bundle branch block configuration. Moreover, aberrant ventricular conduction may involve delays in the left conduction system rather than the right. Since unifocal ventricular premature beats usually have a fixed coupling interval to preceding supraventricular beats, it has been suggested that a variable coupling interval would favor aberrant ventricular conduction. However, ventricular premature beats may have a variable coupling time. It has also been suggested that in atrial fibrillation, ventricular premature beats are more likely to be followed by a pause than aberrant beats, but this distinction is also unreliable. In fact, when Vera et al (23) examined the reliability of the electrocardiogram to differentiate aberrant ventricular conduction from ventricular ectopy, using His bundle electrocardiography, it was found that none of these electrocardiographic findings were accurate.

Polymorphous Ventricular Tachycardia: Torsade de Pointes. One form of ventricular tachycardia deserves special mention because it is so often iatrogenic and its treatment is different from the usual forms of ventricular tachycardia. Polymorphous ventricular tachycardia (torsade de pointes) (Fig. 8) is a form of ventricular tachycardia characterized by a progressive change in the principal direction of the QRS complexes. They appear to undulate progressively positive and negative repetitively.

This form of ventricular tachycardia is most commonly caused by the type I antiarrhythmic drugs quinidine, procainamide, and disopyramide, which prolong the Q-T intervals. It also occurs in patients with congenitally prolonged Q-T intervals and in patients with severe hypokalemia or marked bradycardia. This arrhythmia can be suppressed by overdrive pacing or, sometimes, sympathomimetic amines.

Despite the fact that both A-V block and A-V dissociation are such well-known disorders of impulse transmission, they continue to be a source of confusion. The difficulty is not so much electrocardiographic as conceptual. A-V block and A-V dissociation are distinct and separate arrhythmias (24), and the two terms should not be used synonymously. Older terms such as "interference dissociation," "dissociation with interference," and "primary and secondary A-V block" have been replaced by the simple expression "A-V dissociation," which can be defined concisely and unambiguously. Physiologically, A-V dissociation means independent beating of atria and ventricles. Electrocardiographically, this independence of function is manifested by a totally variable P-R distance. Since A-V dissociation can occur only when the A-V node is refractory, and since refractoriness in the A-V node may be physiologic as well as pathologic, it follows that A-V dissociation may occur when A-V nodal function is "normal" as well as abnormal. On the other hand, A-V block, by definition, is a pathologic state and may be defined as abnormally prolonged conduction in the A-V junction. It is recognized electrocardiographically when P-R intervals exceed 0.2 sec when they should be normal (that is, when atrial impulses reach the A-V node after the termination of its normal refractory period). The two arrhythmias, A-V dissociation and A-V block, may occur separately or simultaneously in both complete and incomplete forms (24). When they occur together, the arrhythmia becomes more complex, but the electrocardiographic criteria for their recognition permit the identification of each arrhythmia separately (Figs. 9 and 10). These differences between A-V dissociation and A-V block are of more than taxonomic interest since the therapy of the two arrhythmias is totally different.

Management

The general principles in the management of cardiac arrhythmias in the elderly are as follows:

- Accurate ECG diagnosis
- Complete clinical diagnosis
- Identification and treatment of precipitating ventricular rate
- Estimate hemodynamic effects:
  - ventricular rate
  - ventricular rhythm
  - atrial contraction
  - sequence of ventricular depolarization
  - stability of pacemakers
  - ventricular function
- Use antiarrhythmic drugs as infrequently and sparingly as possible

The need for accurate, complete clinical and electrocardiographic diagnosis and the identification of specific precipitating factors is self-evident. Utilization of these principles often allows more rational and more effective therapy than specific antiarrhythmic agents.

Fig. 8. Polymorphous ventricular tachycardia, torsade de pointes type.

Consideration of the hemodynamic effects of cardiac arrhythmias permits a more specific set of indications for treatment. Very rapid or very slow ventricular rates reduce cardiac output in subjects over the age of 65. Even in normal hearts, ventricular rates over 160–165/min may reduce diastolic filling time enough to diminish stroke volume and minute flow. Rates below 40–45/min may also reduce flow despite the compensatory increase in stroke volume. In diseased hearts the deleterious effects of rate extremes are magnified because the compensatory mechanisms that adjust contractile function are less effective. Morever, the increase in myocardial oxygen requirements imposed by tachycardia is especially dangerous when coronary reserve is limited by disease. Thus, any of the arrhythmias that result in sustained rapid or slow rates will require treatment.

In contrast to the relative ineffectiveness of available drugs in preventing recurrences of arrhythmias, current modes of treatment are very effective in terminating individual bouts of ectopic tachyarrhythmias. The list of agents is long and well known—digitalis glycosides, parasympathomimetic drugs, type I antiarrhythmic drugs, beta-adrenergic and calcium channel blocking agents, electrical depolarization of the heart. For hemodynamically significant bradyarrhythmias, temporary or permanent iatrogenic pacing is the most reliable form of therapy.

A grossly irregular ventricular rhythm may also reduce cardiac output, especially when the rate is fast. This problem applies whatever the cause of the irregular rhythm (multiple prema-

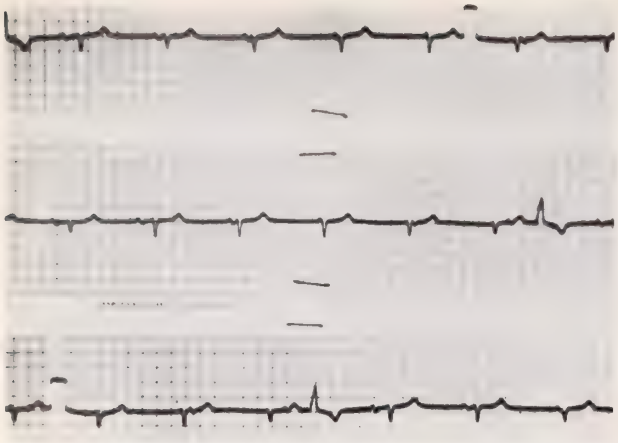


Fig. 9. Incomplete atrioventricular dissociation and incomplete atrioventricular block. Continuous precordial lead V_1. Regular atrial and ventricular cycles are associated with totally variable P-R distance. Intermittent atrioventricular conduction occurs when P wave is located at beginning of T wave, and associated QRS complex displays aberrant ventricular conduction. P-R interval of "ventricular capture" is 0.40 sec, indicating presence of incomplete atrioventricular block.

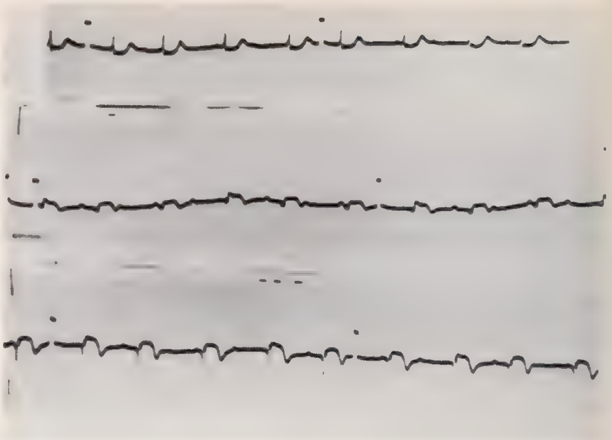


Fig. 10. Incomplete atrioventricular dissociation and incomplete atrioventricular block. Standard leads 1, 2, and 3. Regular sinus rhythm is present. Ventricular rhythm is composed of recurrent sequences of two long R-R intervals followed by short R-R cycle. P-R intervals within short cycles are prolonged but constant. During long R-R intervals, P-R distances are variable and atrial impulses which occur after completion of preceding T wave are not transmitted to ventricles.

ture beats, atrial fibrillation, atrial flutter with varying atrioventricular conduction). However, if the average ventricular rate is less than 100–110 beats/min, and if physical activities are reduced (as they often are for older persons), the irregular rhythm may be well tolerated hemodynamically. Many older persons do not require any drug treatment to maintain physiologic ventricular rates. Most older patients with atrial or ventricular premature beats do not require drug treatment. Properly timed atrial contraction contributes 15%–30% of the ventricular stroke volume. Loss of this component of the stroke volume ordinarily does not significantly compromise overall cardiac function, even though arterial pressure and cardiac output may fall somewhat. However, when the heart muscle is diseased and the myocardial reserve limited, the loss of this amount of stroke volume may cause heart failure. Thus, arrhythmias such as atrial fibrillation, atrioventricular dissociation, and some forms of A-V junctional rhythm may be potentially dangerous in older subjects apart from their effect on ventricular rate. In practice, however, this potential danger is rare, and since most forms of A-V dissociation and A-V junctional rhythm are self-limited and brief, specific treatment is usually not indicated. When A-V dissociation is caused by complete A-V block, iatrogenic pacing is, of course, indicated.

The time course of ventricular depolarization is, theoretically, a factor that may affect overall cardiac function. The normal sequence of ventricular depolarization and contraction results in efficient and maximum emptying of the ventricles during systole. When the time course of depolarization is altered, the time course for shortening of the myocardial muscle bundles is also altered, and stroke volume might be expected to be reduced. Some investigations in experimental animals have confirmed this reduction, but it has not been demonstrated in humans. Thus, disorders of impulse transmission such as bundle branch block and aberrant ventricular conduction do not decrease cardiac output, all other factors being equal.

Finally, the stability of pacemakers may also alter hemodynamic function. Idioventricular pacemakers in the bundle branches and Purkinje system are not only slow but are also unstable, in the sense that their rate may change abruptly, their location may shift, and they may stop functioning altogether, to be replaced by ventricular tachycardia or ventricular fibrillation. This property of ventricular instability is the basis for the Stokes-Adams syndrome in patients with complete A-V block. Related to this problem is the management of the various forms of incomplete bilateral bundle branch block. These disorders of impulse transmission are usually benign clinically and require no treatment. The risk of progression to advanced A-V block is small, 1%–2% per year (25), so that prophylactic pacing is not necessary. When incomplete A-V block complicates bilateral bundle branch block, the risk is greater, and I recommend His bundle electrocardiography to determine the length of the H-V interval. I agree with the recommendation (26) that prophylactic pacing is indicated when the H-V interval is significantly prolonged to 80–100 msec or longer.

Certain biologic properties of elderly persons influence the selection of drug therapy for cardiac arrhythmias (4). Renal function is usually reduced. The hepatic enzyme systems for degrading and metabolizing drugs are less efficient. Hypoxemia is common in the elderly. Autonomic regulatory systems are less effective. These factors make antiarrhythmic drugs potentially more toxic. The metabolic and cardiac demands of older persons are often lower than those of younger persons. The ability of the elderly to comply with complex or multidrug treatment programs is frequently limited. In addition, all the cardioactive agents currently used to treat arrhythmias are inherently dangerous and relatively ineffective in preventing recurrences of arrhythmias. For all these reasons, I believe that the indications of treating arrhythmias in the elderly should be very strong, and that, whenever possible, it is best to omit specific drug treatment or to use antiarrhythmic drugs in reduced doses.

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Sinus Node Dysfunction: New Concepts and Evaluation of Patients with Suspected Sick Sinus Syndrome

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Abnormalities of sinus impulse formation and its conduction to the atrial myocardium can result in a variety of ECG abnormalities. These ECG abnormalities have been collectively referred to as the sick sinus syndrome (SSS) (1). Over the last few years, this syndrome has gained in importance because it accounts for the majority of pacemakers implanted in the United States (2).

The ECG manifestations of the syndrome include varying degrees of sinus bradycardia (usually rates of ≤50 beats/min), sinus arrest, sinoatrial block, and the tachy-brady syndrome. The hallmark of the ECG abnormalities are the manifestations of central nervous system hypoperfusion that result in symptoms of dizziness, lightheadedness, or syncope. In the tachy-brady syndrome the tachycardia component is usually atrial fibrillation, but atrial flutter and paroxysmal atrial tachycardia may also occur. The bradycardia component is a posttachycardia pause which is due to the occurrence of sinus arrest and/or sinoatrial block. During these long pauses, distal pacemakers in the junction and the His-Purkinje system do not readily escape. Whereas the tachycardia component may give rise to symptoms of palpitations or fluttering in the chest or angina pectoris in those who in addition have coronary artery disease, the bradycardia component results in lightheadedness or syncope. Other EGC abnormalities that may be seen in the syndrome include paroxysmal or sustained atrial fibrillation or flutter (3) and bundle branch blocks. The syndrome should be suspected in those patients who do not promptly recover sinus rhythm following cardioversion. An association has been noted in some patients with the hypersensitive carotid sinus syndrome (4, 5).

Etiology of the Syndrome

In the majority of patients, the cause of the sick sinus syndrome is related to degenerative process of the sinus node and atrial myocardium. However, the syndrome has been reported in the following variety of conditions and disease entities (6–8):

- Idiopathic (degenerative)
- Ischemic heart disease
- Cardiomyopathy
- Inflammatory
  - Rheumatic fever
  - Pericarditis
  - Diphtheria
  - Chagas disease
- Infiltrative
  - Amyloid
  - Hemochromatosis
  - Scleroderma
  - Tumor (metastatic)
- Surgical trauma
- Collagen vascular disease
- Familial
- Congenital
- Muscular dystrophies
- Drug induced

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One important entity that should be readily recognized is drug-induced abnormality of sinus node function. Cardioactive drugs such as digitalis glycosides, calcium channel blockers (such as verapamil and diltiazem), beta-adrenergic blocking agents, quinidine, Norpace, and procainamide may induce or unmask an underlying SSS (9–15). Other drugs such as lithium, cimetidine, guanethedine, Aldomet, and clonidine, which are often used in the elderly patient, have been reported to result in sinus node dysfunction.

Electrophysiologic Classification of the Syndrome

Sinus impulse formation and transmission is dependent on a close and complex interaction between intrinsic sinus node automaticity, sinoatrial conduction, and autonomic regulation. The role of the autonomic nervous system in the pathophysiologic mechanism of the syndrome has been delineated only recently. Studies in several independent laboratories (16–19) have demonstrated that, mechanistically, the syndrome can be classified into two types: intrinsic and extrinsic.

In the intrinsic variety, there is an intrinsic abnormality in sinus node function, whereas in the extrinsic variety, the abnormality lies in autonomic regulation. Jordan et al (16) found that the incidence of the intrinsic syndrome was 41%, whereas that of the extrinsic variety was 59%. Desai et al (17) reported that 62% of 21 patients had the extrinsic syndrome, whereas 38% of 21 patients had the intrinsic. We found that approximately 60% of patients had the intrinsic variety, and 40% the extrinsic variety (18, 19). Our studies have also revealed that patients with the intrinsic variety in contrast to the extrinsic variety are older and have a higher incidence of organic heart disease and the tachy-brady syndrome, whereas the incidence of sinus arrest or sinoatrial block is more or less equal in the two varieties.

Thus our findings suggest that in the geriatric age group, the incidence of the intrinsic variety should be higher than the extrinsic variety of syndrome.

Evaluation for Suspected Sinus Node Disorders

Presence of the syndrome can be suggested by the results of a careful history and examination of the ECG. However, in the elderly a variety of medical, central nervous system, and cardiovascular causes can result in syncopal episodes and dizzy spells. Therefore, neither the history alone nor the ECG can be relied on for accurate diagnosis. For the evaluation of the patient with suspected SSS, several noninvasive and invasive tests have been described in recent years.

Noninvasive Tests

Continuous 24-hr Ambulatory ECG Monitoring. A 24-hr ambulatory ECG recording is one of the most important of the noninvasive tests for the syndrome. A 24-hr Holter recording affords collaboration of symptoms with ECG abnormalities. However, it is not unusual to encounter patients who are free of symptoms for long periods. Therefore, symptoms and ECG manifestations of the syndrome may not be readily demonstrated on 24-hr ambulatory Holter. Furthermore, ECG abnormalities alone which occur in patients with SSS may be seen in a substantial number of otherwise asymptomatic subjects (20–23). In a recent study of 106 patients over 75 years of age from a general practice in Sussex, England, Camm et al (24) noted a lower incidence of sinus bradycardia in the elderly than in younger individuals reported in previous studies. Heart rates below 50 beats/min were noted in 11/106 subjects (10%). In 7/11 subjects, sinus bradycardia occurred only during sleep. In 14 patients, atrial and junctional tachyarrhythmias were also noted. However, their subjects cannot be considered normal, since they had a high frequency of syncope, palpitations, dizziness, chest pain, and hypertension, and a high intake of medications. In patients with suspected SSS, Reiffel et al (25) found evidence suggestive of the SSS on 24-hr monitoring in 20 of 51 patients (39%). Recently, Gibson and Heitzman (26) reported on 24-hr Holter results in 1,004 patients 60 years or older with possible SSS. All were referred for syncope. They found that 415 patients (41%) had one or more arrhythmias that were associated with SSS, depending on the definition of the syndrome. However, using stringent criteria of their own, which included (a) sinus bradycardia of a rate of less than 50 beats/min (intermittent, persistent, and not during sleep); (b) sinus pause, sinus arrest, or sinoatrial block of 3.0 sec or longer; (3) junctional rhythm (intermittent and persistent); (4) atrial fibrillation with intermittent slow ventricular response, RR intervals of 2.0 sec or longer; and (5) tachy-brady syndrome, only 32 patients, or 3%, fell into the group of SSS. Furthermore, they found that symptom correlation occurred in only one patient who had syncope secondary to asystole of 7.8 sec and in another who had chest pain secondary to supraventricular tachycardia. They concluded that an open-referral 24-hr ambulatory monitoring service in the elderly patient rarely results in identifying relevant symptom-related arrhythmias in patients with syncope and suspected SSS. Thus, the following inferences can be drawn from these studies: (1) ECG abnormalities suggestive of the SSS may be observed frequently; however, symptom correlation is rare in elderly patients with syncope. (2) A 24-hr ambulatory Holter recording is associated with many asymptomatic arrhythmias that can compound the diagnostic problem in elderly patients and lead to unnecessary therapy. (3) Holter criteria for the diagnosis of SSS should be stringent, and pacemaker therapy should be initially reserved only for those patients in whom a correlation has been noted between ECG abnormalities and symptoms.

Pharmacologic Testing with Atropine and Isoproterenol. The response of the heart rate to two pharmacologic agents, atropine and isoproterenol, has been used to assess sinus rate response in patients with SSS (4, 27, 28). An increase in sinus rate of no more than 90 beats/min is considered abnormal. However, these pharmacologic tests have several limitations: (1) there is no standardization of dosages; (2) dose-response curves in elderly patients are lacking for comparative purposes; (3) the sensitivity and specificity of the tests have not been determined; and (4) a normal response to pharmacologic agents does not preclude the diagnosis of SSS.

Exercise Testing. The sinus rate response to exercise testing has been used in the evaluation of patients with SSS. Reduced heart rate response to exercise in patients with SSS has been described by several investigators. Abbott et al (29) observed that patients with SSS were unable to achieve maximal heart rates comparable to age- and sex-matched controls. However, the sensitivity and specificity of exercise testing remains unknown in the diagnosis of the SSS. One additional and important pitfall of exercise response is that in elderly patients often maximal heart rates cannot be achieved owing to fatigue and poor conditioning.

Carotid Sinus Stimulation. Carotid sinus stimulation should be performed in the workup of elderly patients who present with syncope and/or dizzy spells. The procedure is done by firmly massaging the right and then left carotid artery for a period of up to 10 sec under continuous ECG and blood pressure monitoring. However, prior to carotid massage, auscultation of the carotid arteries for carotid bruits should be performed. Carotid massage should not be performed in patients who have audible carotid bruits. Carotid sinus hypersensitivity is indicated when a pause longer than 3 sec occurs during carotid massage. Although association between carotid sinus hypersensitivity and the presence of SSS has been reported, these two syndromes more often exist as separate entities.

Electrophysiologic Evaluation of Sinus Node Dysfunction

Indications. Electrophysiologic assessment of sinus node function is indicated in the following:

1. Patients with suspected SSS and elderly patients with syncope and frequent dizzy spells in whom 24-hr ambulatory Holter monitoring does not provide the diagnosis or correlation with symptoms and ECG abnormalities. Of 49 male patients ≥65 years of age evaluated for syncope in our laboratory, 57% had electrophysiologic abnormalities suggestive of sinus node dysfunction.
2. Elderly patients who develop signs and symptoms of sinus node dysfunction on small dosages of cardiac drugs like digitalis, beta-adrenergic blockers, calcium channel blockers, and type I antiarrhythmic agents.
3. Patients with paroxysmal atrial flutter/fibrillation or paroxysmal atrial tachycardia who either do not have the bradycardia component or are asymptomatic from the latter and in whom antiarrhythmic therapy is contemplated to treat the tachyarrhythmia.

Tests. Electrophysiologic tests for evaluation of sinus node function are invasive in character and involve the introduction of one or more electrode catheters in the right atrium both for recording of intracardiac electrical activity and for stimulation. These electrophysiologic tests include the following: (a) sinus node recovery time, (b) sinoatrial conduction time, (c) determination of intrinsic heart rate and sinus node recovery time following pharmacologic autonomic blockade, and (d) assessment of AV nodal and His-Purkinje conduction.

Sinus Node Recovery Time. Sinus node recovery time (4, 30) (SNRT) is assessed by pacing the atrium at rates above the spontaneous rate for a period of 1 min (range = 30 sec to 2 min), after which atrial pacing is abruptly terminated. Overdrive atrial pacing should be performed at multiple pacing rates in increments of 10–20 beats/min up to a rate of 200 beats/min. SNRT is

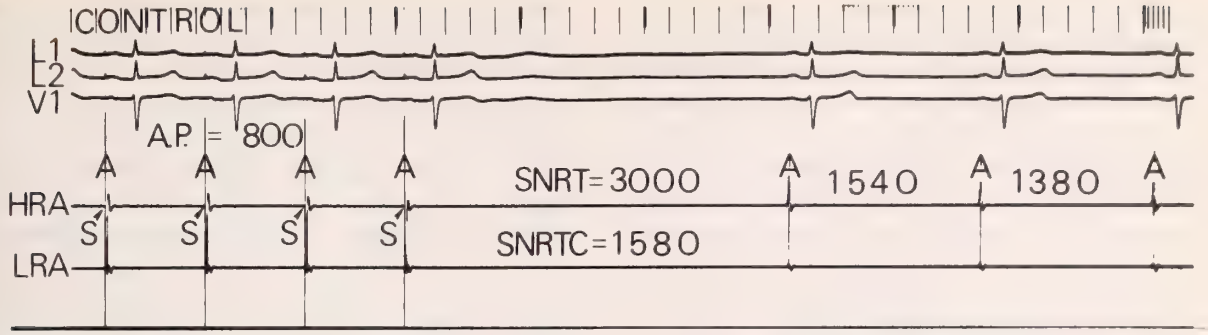


Fig. 1. Assessment of sinus node recovery time (SNRT) in a patient with episodes of lightheadedness, syncope, and sinus bradycardia. From top to bottom: ECG leads 2 and V_1 and intracardiac recordings from high right atrium (HRA) and His bundle (HBE). Last 4 beats of overdrive atrial pacing at cycle length of 800 msec performed for 1 min are shown, following which pacing is abruptly terminated. Corrected SNRT (SNRTC) was abnormal (1,580 msec).

measured as the interval from the last paced atrial beat to the first spontaneous atrial deflection (A wave) or P wave of sinus origin (Fig. 1). The longest SNRT obtained at any pacing rate is taken as the representative SNRT. The SNRT has been expressed as the corrected SNRT (30) (SNRTc), which is obtained by subtracting the SNRT from the basic sinus cycle length (Fig. 1) or as a ratio of the sinus cycle length (31). Most laboratories use the SNRTc to determine an abnormal recovery time. A wide range of normal values (1200–1740 msec) for SNRT and SNRTc (375–525 msec) are reported using the mean value plus two standard deviations as the upper limit of normal for each study. In our laboratory a value of >450 msec (SNRTc) is considered abnormal. An abnormal SNRT or SNRTc has been noted in 40%–93% of patients suspected of having the syndrome (4, 19, 30, 32). This wide variability in abnormal SNRT is probably related to variability in patient selection and the severity of the syndrome. In addition, other factors—such as shift of the sinus pacemaker complex from a dominant to a subsidiary site, which has been recently demonstrated in our laboratory, induction of sinus node reentry, and incomplete suppression of the sinus node due to entrance block—could all influence measurement of SNRT. At times the administration of atropine (33) may enhance atriosinus conduction or abolish entrance block resulting in a longer recovery time.

Until recently, the observation of an abnormally prolonged SNRT was taken to imply that sinus node automaticity was abnormal (4, 30). However, our recent studies (34) have shown that these assumptions are not necessarily true. Studies utilizing direct recordings of sinus nodal potentials in humans have demonstrated that the SNRT assessed by indirect methods described above is a reflection of sinus nodal automaticity as well as sinoatrial conduction (12). Gomes et al (34) have used direct recordings of sinus activity to assess direct SNRT. These studies (12) have shown that, first, direct SNRT is significantly longer in patients with the syndrome (1263 ± 256 msec) than in patients without it (779 ± 89 msec). Second, SACT is prolonged following overdrive atrial pacing both in patients with and without the syndrome, but the degree of prolongation is greater in patients with it. Third, prolongation of indirect SNRT in patients with the syndrome is accounted for in the majority of instances by prolongation of sinoatrial conduction time for the first postpacing sinus beat. Asseman et al (35) also noted persistent sinus nodal electrical activity during long atrial pauses following overdrive pacing. They suggested that these pauses were the result of sinoatrial conduction block rather than depression of sinus nodal automaticity. Thus, these studies have suggested that although patients with the syndrome are likely to have abnormalities of sinus nodal automaticity and sinoatrial conduction, abnormalities of conduction could be clinically more significant than those of automaticity.

Sinoatrial Conduction Time. Sinoatrial conduction time (SACT) is the time it takes for the sinus impulse to depolarize the atrium. This time can be assessed by indirect and direct methods. The indirect methods include the premature stimulation method (36) and the continuous pacing method (37), both taking into account the same several assumptions. The direct method involves recording a sinus node potential (38).

The premature stimulation method was originally proposed by Strauss and co-workers (36). According to this method, programmed premature stimuli are introduced late in diastole after every eighth spontaneous sinus beat and moved progressively earlier until atrial muscle refractoriness. The A_1A_1 is the spontaneous sinus cycle preceding the premature atrial stimulus; A_1A_2 is the coupling interval of the premature atrial stimulus; and A_2A_3 is the return cycle or the post-extrasystolic pause. On plotting the normalized test cycle (A_1A_2/A_1A_1) against the return cycle (A_2A_3/A_1A_1), Strauss and co-workers observed two types of responses: (1) a fully compensatory pause in response to premature stimuli late in diastole and (2) a noncompensatory pause; i.e., the A_2A_3 interval was no longer fully compensatory but greater than the spontaneous A_1A_1 cycle. It was postulated that the sinus node was reset in the zone of noncompensation. The range over which the return cycle (A_2A_3) exceeds spontaneous cycles (A_1A_1) in the zone of reset reflects conduction time of the atrial impulse into the atriosinus and sinoatrial direction. Half the difference between the return (A_2A_3) and spontaneous cycle (A_1A_1) is the unidirectional SACT.

The continuous pacing method was introduced by Narula and co-workers (30). Using this indirect technique, the atria are paced at a rate slightly faster (<10 beats/min) that the sinus rate, generally for eight beats, after which pacing is terminated. SACT is calculated by subtracting the mean sinus cycle from the interval between the last paced atrial electrogram and the first escape sinus cycle (Fig. 2). Division of this number by two gives the unidirectional SACT.

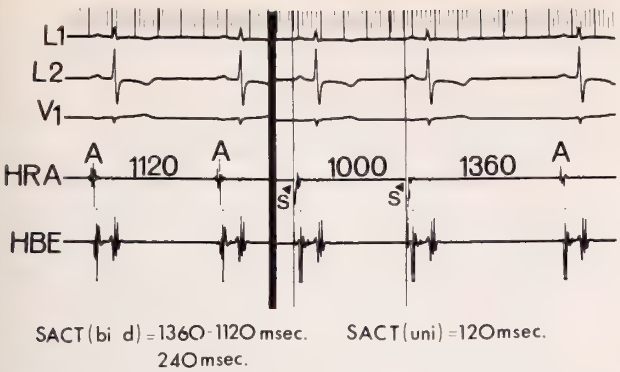
Normal values for SACT have ranged from 50 to 120 msec. Most laboratories usually consider a value of ≥120 msec for unidirectional SACT abnormal.

The direct method of measuring SACT involves recording a sinus node potential. The electrophysiologic bases of recording a sinus node potential in humans are the microelectrode and extracellular studies of sinus node potentials in the animal heart performed by Cramer et al in 1978 (39). To record a sinus node electrogram (38, 40, 41), a number 6 French quadripolar electrode catheter with 10-mm interelectrode distance is inserted via the femoral vein and positioned at the junction of the superior vena cava and right atrial endocardium. The distal poles of the catheter are utilized to record a sinus node electrogram. The sinus node electrogram is obtained by using low pass filter frequencies of 0.1–50 Hz and high gain amplification of 50–100 μv/cm.

Of the three methods currently available to assess SACT, the continuous pacing method is the simplest and least time consuming, whereas the premature stimulation method is more complex in its methodology and calculation. The direct method (Fig. 3) is dependent on obtaining close catheter contact with the atrial endocardium overlying the sinus node region and can be successfully obtained in 80%–90% of patients. It is, however, the most accurate method and does not involve several assumptions that both the premature stimulation and continuous pacing methods take into account. On the sinus node electrogram, direct SACT is measured from the onset of the upstroke slope to the onset of activation of the atrium on the sinus node electrogram or the high right atrial electrogram. Reiffel et al reported normal values for direct SACT of 46–116 msec, and Gomes et al (38) reported normal values of 50–112 msec. In addition, we have found that the direct method provides a better separation of patients with the sick sinus syndrome from those without it. The incidence of abnormal prolongation of SACT in patients with and without the syndrome has varied considerably when measured by the indirect methods. Dhingra and co-workers (42) found a 2% incidence of abnormal SACT in 418 patients without sinus node dysfunction and in 29% of 52 patients with the syndrome. Strauss and co-workers (43) reported abnormal values in 38% of patients with it whereas Breithardt and co-workers (44) reported abnormal values in 45% of 41 such patients. We also have reported abnormal values in 41% of 22 patients with the syndrome. However, we found that a greater proportion of patients (74%) with the extrinsic syndrome had prolonged SACTs. In contrast, only 23% of patients with the intrinsic syndrome had abnormally prolonged SACTs (32).

Sensitivity and Specificity. Breithardt and co-workers (44) correlated prolongation of SNRT and SACT with specific electrocardiographic abnormalities in patients with SSS. They found that patients with symptomatic sinus bradycardia had significantly longer values of SACT and SNRT than did asymptomatic subjects. Patients with spontaneous SA block demonstrated longer SACT values whereas those with the tachy-brady syndrome had longer SNRT values. Breithardt et al observed that SNRT was a more sensitive parameter. However, the use of SNRT and SACT increased the diagnostic sensitivity of electrophysiologic testing.

With colleagues, I studied sinus node function in a total of 148 patients who ranged in age from 19 to 94 years: 71 with symptomatic SSS (Group I); 10 with paroxysmal atrial fibrillation or flutter without the bradycardia component (Group II); 17 with sinus bradycardia along (Group III); 50 who



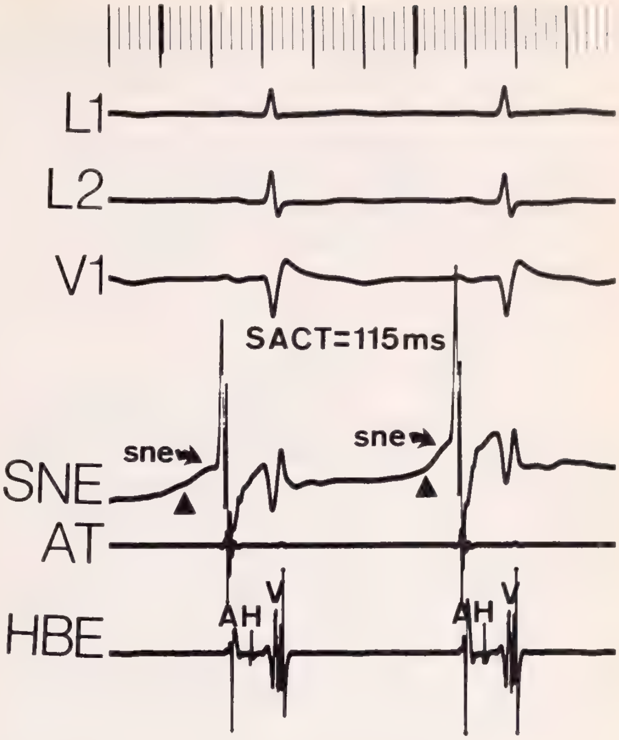


Fig. 2. Left Continuous pacing method for assessment of SACT. From top to bottom: ECG leads 1, 2, and V_1 and intracardiac electrograms from HRA and HBE. Atrium is paced for 8 beats, after which atrial pacing is abruptly terminated. SACT is calculated as difference between interval of return cycle (1,360) and basic cycle (1,120). Bidirectional SACT is 240 msec and unidirectional SACT is half this value.

Fig. 3. Right Sinus node electrogram from a patient with sick sinus syndrome. From top to bottom: ECG leads 1, 2, and V_1 sinus node electrogram (SNE), intracardial atrial (AT), and His bundle electrogram (HBE). SNE reveals clear diastolic and upstroke slope. Direct sinoatrial conduction time (SACT) is measured from onset of upstroke slope (straight arrow) to atrial electrogram. Direct SACT was 115 msec.

yielded no evidence of sinus node dysfunction (Group IV). Abnormal sinus node function was defined as the presence of an abnormally prolonged SNRTc and/or SACT. Abnormal sinus node function was noted in 81.6% of Group I, 50% of Group II, 47% of Group III, and 12% of Group IV patients. On the basis of our findings in Group I and Group IV, assessment of sinus node function by determination of SNRTc and SACT has a sensitivity of 82% and a specificity of 88%. Of additional importance is the finding that electrophysiologic evidence of abnormal sinus node function is dependent on the type and grade of sinus node dysfunction.

Determination of Intrinsic Heart Rate and Sinus Node Recovery Time after Pharmacologic Autonomic Blockade. Intrinsic heart rate (IHR) is determined following pharmacologic autonomic blockade with propranolol (0.2 mg/kg body weight) and atropine sulfate (0.04 mg/kg body weight). The maximum spontaneous sinus rate observed 5 min after autonomic blockade is the intrinsic heart rate. Normal values for IHR can be determined by utilizing the linear regression equation derived by Jose (45, 46) relating predicted IHR to age. Thus predicted IHR = 118.1 (0.57 × age). For subjects less than 45 years of age, the 95% confidence limit is predicted IHR ± 18% and for subjects greater than 45 years of age the 95% confidence limit is predicted IHR ± 14%. An IHR falling within two standard deviations of the predicted IHR is considered normal, whereas an IHR falling below and outside the 95% confidence limit of predicted IHR is considered abnormal. The determination of IHR and SNRT prior to and following pharmacologic autonomic blockade can provide an understanding of the mechanism of the SSS (16–19) and increase the sensitivity of the SNRT (19). Patients with an abnormal IHR have intrinsic SSS, whereas those with a normal IHR have the extrinsic variety of SSS. In patients with an extrinsic SSS who have an abnormal SNRT prior to autonomic blockade, SNRT normalizes following autonomic blockade. This subgroup of patients classically represents sinus node dysfunction due to abnormally exaggerated parasympathetic tone. The majority of patients with intrinsic SSS have an abnormal SNRT prior to autonomic blockade. However, in a minority of patients with instrinsic SSS, the SNRT becomes abnormal only after autonomic blockade. Thus, determination of SNRT following autonomic blockade increases the sensitivity of SNRT in patients with intrinsic SSS.

Evaluation of AV Nodal and His-Purkinje Conduction. Patients with suspected SSS who have prolongation of the PR interval, bundle branch block, or bifascicular block should have evaluation of AV nodal and His-Purkinje conduction by rapid atrial pacing starting at rates above sinus rates in increments of 10–20 beats up to a rate of 200 beats/min. In some of these patients the symptoms of syncope may be related to the occurrence of paroxsymal AV block rather than due to sinus node dysfunction. Furthermore, evaluation of AV nodal and His-Purkinje system conduction is needed in patients in whom permanent atrial pacing is contemplated as the modality of therapy.

Therapy

No therapy is recommended for asymptomatic elderly subjects with electrocardiographic manifestations of sick sinus syndrome. Antiarrhythmic agents to suppress paroxysmal atrial fibrillation and/or flutter in asymptomatic patients should be used, if at all, with extreme caution, since these agents have the propensity of compounding the bradyarrhythmia. The use of anticoagulants is justified in patients with tachybrady syndrome if the tachycardia component is atrial fibrillation (47, 48).

Permanent pacing remains the definitive treatment for symptomatic patients with the syndrome. Pacing relieves the symptoms resulting from the bradycardia and allows treatment of the tachyarrhythmias with antiarrhythmic agents. Ventricular demand (VVI) dual chamber pacemakers and atrial demand pacemakers (AAI) have all been recommended in the SSS. AAI pacemakers are currently favored in the absence of AV conduction disease (49, 50). In addition, these pacemakers can increase cardiac output by preserving atrial contraction, which is of benefit to patients with left ventricular dysfunction. In patients with left ventricular dysfunction and AV conduction abnormalities, dual-chamber pacemakers are recommended. Similarly, patients with hypersensitive carotid sinus syndrome with a vasodepressor component do better with dual chamber pacing.

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The Role of Early Radionuclide Ejection Fraction in Predicting Early Mortality after Acute Myocardial Infarction in the Elderly

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Abstract

We prospectively studied 36 elderly patients, 70 years of age or older, who were Killip class I or II at presentation, to analyze for determinants of in-hospital mortality after acute myocardial infarction. Age, sex, location of Q-wave infarction, and peak CK elevation were not found to be significantly associated with early mortality. Differentiation between Killip class I or II was not predictive of early mortality. Radionuclide ejection fraction, obtained within 24 hr of onset of chest pain, disclosed a significant association between early mortality and ejection fraction less than or equal to 30% ($p < 0.025$) or 40% ($p < 0.05$). Utilizing these ejection fraction endpoints, we noted 62.5% early mortality among patients with ejection fraction less than or equal to 30%, compared to 9% early mortality among patients with ejection fraction greater than 40%. Radionuclide ejection fraction early in the course of myocardial infarction in the elderly can determine both high- and low-risk groups. Aggressive research interventions, such as thrombolysis, angioplasty, or urgent bypass grafting, should not be applied to low-risk groups in the elderly.

Risk stratification in acute myocardial infarction has been extensively studied in the past 20 years. Early studies by Killip and Kimball (1) and Norris et al (2) stressed that certain early clinical factors were capable of predicting in-hospital outcome, including age, location of infarct, and either clinical or radiographic evidence of congestive heart failure. Radionuclide evaluation in early acute myocardial infarction has been shown to be related to short-term prognosis (3, 4). We have previously shown in a younger age group that initial ejection fraction and Killip class were the factors most closely associated with early mortality in acute myocardial infarction (5). Recent prospective studies have been concerned with risk stratification after discharge and have noted that the degree of left ventricular dysfunction and the presence of ventricular arrhythmias were the prime predictors of myocardial events after discharge (6–11).

Although age was noted to be a risk factor in some of the early studies, most recent studies have excluded the elderly in their study design (6, 7, 10, 11). Relatively few studies have looked at prognosis after myocardial infarction in the elderly (8, 12, 13); those studies that have examined prognosis have not included radionuclide data.

Previously, modes of management other than standard medical therapy of coronary artery disease in the elderly were believed to be more or

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less contraindicated, owing to the increased morbidity and mortality associated with coronary artery bypass surgery in older patients (14–16). Recent reports, however, have stressed that with improvements in operative technique and myocardial preservation, myocardial revascularization can be more safely performed in the elderly (17–19). Consideration is also being given to other methods of therapy in acute myocardial infarction, including percutaneous transluminal coronary angioplasty, thrombolytic therapy, or a combination of both (20–26). Hence, we elected to evaluate risk factors in the elderly which might predict high-risk patients who could potentially benefit from more aggressive management. We also hoped to determine low-risk groups, in whom more aggressive management may be less beneficial.

We prospectively studied a group of 36 patients, 70 years of age or older, to analyze early determinants of prognosis. We limited our study to those patients who were either Killip class I or II, because these patients, as a group, have been shown to have a good prognosis. Further differentiation of subsets of the elderly by risk factors might disclose a high-risk subgroup who might benefit from early aggressive management. This was the purpose of this study.

Study Group and Methods

Patient Population. Patients were enrolled prospectively as part of an ongoing research protocol involving acute myocardial infarction. Patients in this arm of the protocol were required to be age 70 or older, have an acute Q-wave infarction, and clinically determined to be either Killip class I or II at the time of admission. Exclusion criteria included non-Q-wave myocardial infarction, Killip class III or IV, or bundle branch block obscuring the location of the infarction.

Definitions. Patients were classified according to clinical evidence of left ventricular dysfunction (Killip class). Class I was defined as the absence of signs of left ventricular failure. Class II included those patients with mild to moderate left ventricular failure, as evidenced by the presence of pulmonary rales or an S3 gallop.

The designation of Q-wave myocardial infarction required the presence of all of the following: (a) a clinical syndrome of myocardial infarction that included prolonged chest pain of greater than 30 min, (b) electrocardiographic evidence of acute myocardial infarction associated with the development of Q-waves, and (c) a peak serum creatine kinase level demonstrating a twofold rise above the upper limits of normal.

The location of the infarction was defined as anterior if Q-wave development was noted in leads I, aVL, or V1 to V6, or inferior if Q-wave development was noted in leads II, III, or aVF. "Early mortality" was defined as death occurring during the patient's initial hospitalization for acute myocardial infarction.

Radionuclide Evaluation. Technetium-99m equilibrium-gated radionuclide ventriculography was performed in all 36 patients within 24 hr of the onset of chest pain (9.6 ± 6.1 hr). Image acquisition was obtained with a gamma camera (Siemens) linked to a dedicated PDP 11/60 computer (Digital Equipment Corporation). Equilibrium-gated blood pool imaging of the left ventricle was accomplished with the patient in the modified left anterior oblique 45-degree position. According to the method of Pavel et al (27), patients received an initial intravenous injection of 7.7 mg of stannous pyrophosphate (Mallinckrodt) in 1 ml of physiologic saline solution. Twenty minutes later the patient received an intravenous injection of 20 mCi of technetium-99m pertechnetate (New England Nuclear). Data collection in the gated synchronized mode was begun 10 min after administration of the radionuclide.

Statistical Analysis. Early mortality after myocardial infarction was evaluted as a discrete endpoint. Left ventricular ejection fraction was dichotomized using standard endpoints utilized in previous studies (6, 7, 9, 11). Individual risk factors were evaluated for an association with mortality by computation of a 2 × 2 matrix chi square. Differences between groups of continuous variables were evaluated using the unpaired two-tailed Student's *t* test. Mean data are expressed as the mean ± the standard deviation.

Results

The 36 elderly patients in this study were divided into two groups, those who survived while in hospital and those who did not. We found that neither age, sex, previous myocardial infarction, nor Killip class at the time of presentation was associated with early mortality (Table 1). Of the electrocardiographic, enzymatic, and radionuclide characteristics (Table 2), only the left ventricular ejection fraction, obtained within 24 hr of the onset of chest pain, was found to be significantly different between the two groups. Because of this finding, left ventricular ejection fraction was dichotomized at two commonly used points, 30% and 40%, to assess the predictive value of

TABLE 1
Clinical Characteristics

Group	n	Age	Sex M	 F	Previous MI	Killip class I	 II
Survivors	27	74.5 ±3.9	18	9	2	19	8
In-hospital deaths	9	73.3 ±4.1	7	2	3	5	4
p value		NS	NS		NS	NS	

F, female; M, male; *n*, number of patients; previous MI, number of patients with history of previous myocardial infarction.

early ejection fraction in determining early mortality.

The sensitivity, specificity, predictive values, and relative risk of left ventricular ejection fractions of less than or equal to 30% and 40% in predicting early mortality are shown in Table 3. The specificity of the 30% ejection fraction endpoint is higher than that of the 40% endpoint, whereas the 40% ejection fraction has a higher sensitivity. The predictive value of a positive response, that is, a diminished ejection fraction being associated with early mortality, was 63% using the 30% endpoint and 47% using the 40% endpoint. Notable was the predictive value of a negative result, that is, a relatively normal ejection fraction associated with survivorship during hospitalization for acute infarction, which was 86% for ejection fraction endpoints of 30% and 90% for the 40% endpoint.

Mortality was further analyzed using the 30% and 40% ejection fraction endpoints. We found that an ejection fraction of less than or equal to 30% was significantly associated with early mortality ($p < 0.025$). The mortality of patients in this group was 62.5% (Table 4), whereas ejection fraction of greater than 30% was associated with only 14.3% mortality. Utilizing the 40% cut point, early mortality was associated with an ejection fraction of 40% or less ($p < 0.05$) and was 47%, compared to 9.5% in the group with an ejection fraction of greater than 40%.

TABLE 3
Ability of Ejection Fraction to Predict In-Hospital Mortality

	LVEF 30%	LVEF 40%
Sensitivity	56%	78%
Specificity	89%	70%
Positive pred. value	63%	47%
Negative pred. value	86%	90%
Risk ratio	4.37	4.90

LVEF, left ventricular ejection fraction; negative pred. value, predictive value of a negative test; positive pred. value, predictive value of a positive test.

TABLE 2
Electrocardiographic, Enzymatic, and Radionuclide Characteristics

Group	n	Location of MI Ant.	 Inf.	Peak CK	LVEF
Survivors	27	10	17	1379 ±1044	47.5 ±12.3
In-hospital deaths	9	6	3	1761 ±1041	29.6 ±11.0
p value		NS		NS	<0.05

Ant., anterior myocardial infarction; Inf., inferior myocardial infarction; location of MI, electrocardiographic location of myocardial infarction; LVEF, left ventricular ejection fraction; *n*, number of patients.

Discussion

There have been many prospective studies of the risk of a significant cardiac event following myocardial infarction, but the vast majority have excluded the elderly patient (6, 7, 10, 11). We evaluated a group of patients 70 years or older to note the associations of myocardial infarction with early mortality and hence to determine whether certain subgroups are at increased risk and therefore might benefit from more aggressive forms of management.

Of the clinical factors evaluated, we found that only the initial left ventricular ejection fraction, obtained within 24 hr of the onset of chest pain, was predictive of survival during hospitalization for acute myocardial infarction. Because of the relatively small number of patients in our study group, 36, we could not identify other prognostically significant risk factors less strongly associated with mortality than low ejection fraction and requiring a larger study group to be detected.

Since diminished initial ejection fraction was found to be associated with early mortality, we further analyzed our data with respect to several

TABLE 4
Mortality Associated with Early Left Ventricular Ejection Fraction

	LVEF <= 30%	LVEF > 30%
Mortality (%)	62.5%	14.3%
	LVEF <= 40%	LVEF > 40%
Mortality (%)	47%	9%

LVEF, left ventricular ejection fraction.

commonly used ejection fraction endpoints, namely, 30% and 40%. We noted that with the 30% ejection fraction endpoint, the specificity of a diminished ejection fraction being associated with early mortality was a striking 89%. Moreover, if the ejection fraction was greater than 30%, a correlation was noted with survival, as evidenced by the predictive value of a negative test of 86%. Similar findings were noted with the 40% endpoint, with the exception of some decrease in specificity with an improvement in sensitivity.

By identifying groups of patients at both high and low risk of early mortality, the use of new interventional therapies in patients who have sustained acute myocardial infarction can be more rationally applied. Low-risk patients should no longer be submitted to the potential morbidity and mortality of thrombolytic therapy, transluminal angioplasty, or coronary artery bypass surgery. For example, the incidence of major bleeding with various forms of thrombolytic therapy, which ranges between 6% and 13% (28, 29), could be avoided in low-risk groups.

In summary, we evaluated clinical, enzymatic, electrocardiographic, and radionuclide data in 36 elderly patients who had Killip class I or II Q-wave myocardial infarction. We noted an early mortality of 25% in this group of patients. Of all factors evaluated, only a diminished ejection fraction, obtained within 24 hr of the onset of chest pain, was associated with early mortality. Conversely, an ejection fraction of greater than 30% was predictive of survival during that hospital admission. By subsetting both high- and low-risk patients, a more rational approach can be undertaken to experimental interventional therapy in acute myocardial infarction in the elderly.

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The Management of Depression and Anxiety Following Myocardial Infarction

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The morbidity associated with coronary artery disease (CAD) and myocardial infarction (MI) has both physical and emotional manifestations. Since over 500,000 people each year in this country survive MI (1), the recognition and management of the complications of MI is essential (2). This article focuses on the psychiatric considerations that surround MI, encompassing five stages: prehospital course; time in the emergency ward; coronary care unit stay; transfer to the step-down unit; and posthospital course.

Prehospital Course

In recent years recognition and reduction of the risk factors associated with development of CAD has come to the forefront of preventive medicine (3, 4). While some of these risk factors are not modifiable (advancing age, the presence of diabetes, family history of CAD), others can be reduced (obesity, hypertension, cigarette smoking, elevated cholesterol levels). Psychological risk factors have also been implicated in the genesis of CAD (5–8), MI, ventricular ectopy (9–11), and sudden death (12, 13). Holmes and Rahe (14) proposed a theory which stated that the accumulation of life stress, as measured by life change units, was associated with the development of illness. The nature of the stress, or life change, could be seen as positive (a job promotion) or negative (the death of a spouse). Type A (coronary-prone) behavior patterns, characterized by a sense of pressure by time, have also been associated with a higher incidence of CAD in general (7), and with ventricular ectopy in those patients with CAD (11). As a result, numerous attempts to modify Type A behavior patterns have been made (15, 16), including the use of behavior therapy, individual psychotherapy, and support groups for post-MI patients (17, 18).

A major factor accounting for the high mortality associated with MI is the period of delay between the onset of symptoms and the person's arrival at an emergency ward. Most MI deaths result from arrhythmias, which occur within the first 12 hr after the MI (19). Therefore, a decrease in the time between the onset of chest pain and the arrival of individuals at the emergency ward for medical attention would save lives. Denial frequently accounts for the delay in receiving medical help following the onset of chest pain. Used in its psychological sense, denial is defined as "the conscious or unconscious repudiation of all or part of the total available meaning of an event to allay fear, anxiety, or other unpleasant affects" (20). This definition distinguishes denial from a genuine failure to recognize the symptoms of a cardiac event. Hackett and Cassem (21) found that for MI patients, the mean delay time between onset of chest pain and arrival at the emergency ward was 3.9 hr. However, approximately one-third of their patients arrived more than 6 hr after chest pain began. Delays were decreased as a person's symptoms increased and were diminished by the attention of an interested, nonrelated person. As a result, education about the signs and symptoms of MI for patients with CAD as well as patient contacts should help to overcome patient denial and facilitate rapid transport of symptomatic patients to the hospital. Such a strategy would be expected to decrease the mortality that results from MI (22).

Time in the Emergency Ward

Upon arrival in the emergency ward, even those patients who are familiar with the practice

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of medicine are faced with an often disturbing rite of passage. Typically, patients with chest pain are triaged to an area of the ward in which the evaluation of cardiac patients can be expedited. Here the onslaught of medical personnel and technology begins. A history is obtained, a physical examination is rapidly performed, an intravenous line is placed, blood samples are drawn, an electrocardiogram is taken, and a cardiac monitor is set up at the bedside. Many patients become anxious when confronted with this ritual. Anxiety is often compounded by the presence of ongoing pain, shortness of breath, the recollection of previous admissions with similar symptoms, and fear of death. Uncertainty about one's outcome may also be exacerbated by the arrival of the priest to administer the sacraments of the sick (23). While he or she is left alone for periods of time between examinations, a patient's anxiety may build. Family members are often left waiting, frequently without benefit of even limited explanations. This failure to provide the family and the patient with adequate information contributes to their sense of dread and helplessness. Treatment of this fear and anxiety is usually limited to explanations about one's condition, reassurance, and the administration of medications (such as narcotics and nitrates) to combat chest pain and ischemia. Although the initiation of anxiolytics (for example, benzodiazepines) should begin in the emergency ward, it is usually deferred until the patient's arrival in the CCU.

The Coronary Care Unit Stay

Typically, after a brisk stretcher ride through the corridors of the hospital, with a portable cardiac monitor and physician escort, the cardiac patient arrives in the ICU/CCU and is greeted by a bombardment of stimuli: alarms, buzzers, whooshes of respirators, and flashing lights (24). This does little to dampen anxiety. Once the patient is settled into the unit, the most common psychiatric problems encountered are anxiety, depression, the manifestations of character problems, and delirium (25).

Anxiety

Range, Timing, and Manifestations. Cassem and Hackett (25), in a study of psychiatric consultations to a CCU at the Massachusetts General Hospital, found that requests to treat anxiety were most frequently made during the first two days of a patient's stay in the CCU (see Fig. 1). Anxiety in the CCU is frequently manifest by a subjective sense of tension, apprehension, or fear, and by objective measures which include tachycardia, tachypnea, diaphoresis, insomnia, hypertension, and ventricular ectopy. Common sources of anxiety include the threat of death and disability. These fears are often magnified by the enforced limitation on activity in the unit. This restriction is imposed so that unnecessary work is not done by the injured heart. Unfortunately this limitation leads to a further sense of weakness, which can be misperceived by the patient as proof of disability.

Another cause for anxiety in the unit is the chance to witness a cardiac arrest. While many patients have misconceptions (which may lead to a superficial sense of security) about the course of events that occur during such an event (2), most patients who have witnessed a cardiac arrest prefer to avoid having such an opportunity again in the future. In one study, all patients who had witnessed a cardiac arrest in the CCU opted for a single-bed room should they ever need readmission to the hospital (26).

An additional factor that can generate anxiety is the standard practice of ward rounds. A statistically higher incidence of periinfarction complications in a Scandinavian CCU was noted during the time surrounding attending rounds in the CCU (27). Theoretically, a surge in catecholamine output, which coincides with a patient's anticipation of hearing the physician's opinion or verdict, was responsible for this result. Therefore, forewarning patients about the routine nature of daily rounds may protect against their potentially toxic effects.

Treatment. Although most post-infarct patients in the unit are anxious, many go without the benefit of receiving any anxiolytic medication (28, 29). In a recent study at the MGH (30), only two-thirds of all patients admitted to a CCU had any anxiolytic or hypnotic medications prescribed during their entire course in the unit. When these agents were prescribed, a majority of the orders were written as p.r.n., rather than as fixed-dose schedules. Moreover, only 15% of p.r.n. and 85% of fixed doses were administered to the patients. One reason for this underprescription of anxiolytics was the failure by staff to recognize the symptoms of anxiety in their patients. When anxiety was detected, the fear of both the patient and the physician that a dependency on medications would ensue further limited the prescription of anxiolytics. In a minority of patients the use of agents known to produce sedation is minimized so that a patient's overall mental status and level of consciousness can be observed.

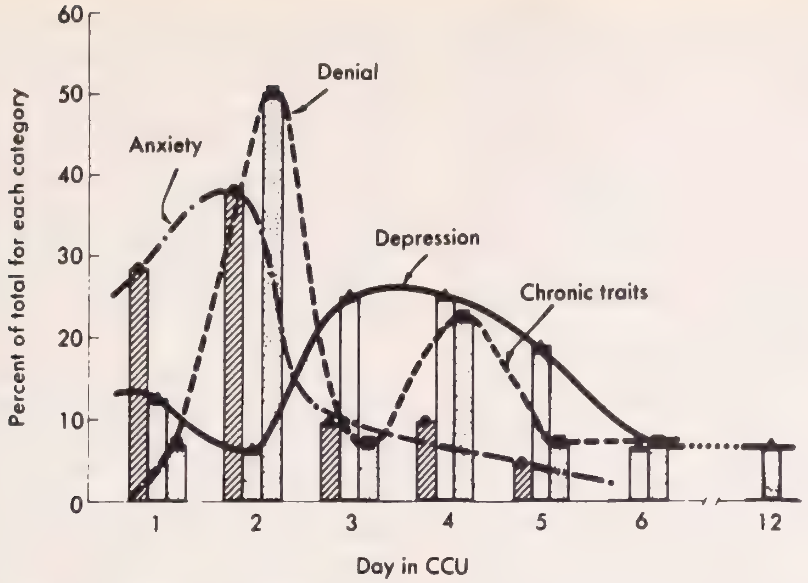

Fig. 1. Hypothetical sequence of emotional and behavioral reactions of a coronary care unit patient, derived from the frequency of psychiatric consultation for each category of reaction. Reprinted with permission from Cassem NH, Hackett TP. Psychiatric consultation in a coronary care unit. Ann Intern Med 1971; 75: 9–14.

When medication is used to treat anxiety, it is usually well tolerated. Only a small percentage of MI patients in another study objected to being oversedated, whereupon the dose of prescribed anxiolytic medication was decreased (31).

Treatment of the symptoms of anxiety should improve disrupted sleep patterns, lower circulating catecholamine levels (thereby helping to avoid the genesis of arrhythmias in ischemic and injured myocardium), and decrease emotional reactivity to fear and conflict. Over the last decade the benzodiazepines have replaced the barbiturates as the drugs of choice in the treatment of anxiety (32). Rational prescribing of these agents is dependent on a knowledge of their therapeutic effects and their side effects. Each of them is anxiolytic and produces drowsiness. However, they differ in potency, rapidity and duration of action, and level of sedation (Table 1). Tailoring the choice of agent to the clinical situation makes good clinical sense, rather than relying on one standard agent for all situations.

Commonly used short-acting (half-life 5–20 hr) benzodiazepines include oxazepam, lorazepam, temazepam, and alprazolam; intermediate-acting benzodiazepines include diazepam and chlordiazepoxide; and long-acting benzodiazepines include clorazepate and flurazepam. It is also important to consider that the duration of action of these agents increases substantially as the age of a patient advances. Therefore, the elderly usually require lower doses, at less frequent intervals, than do younger persons. In addition, many of these agents are oxidized to benzodiazepine metabolites that are pharmacologically active and have even longer half-lives.

Depression

Range, Timing, and Manifestation. Requests for the assessment of depression are most common on the third and fourth days after admission (25). Depression, like anxiety, is fueled by limitations on activity, by weakness, and by fear. Fears of disability and a loss of potency (taken in its broadest, rather than in its sexual, sense) arise as the psychological defense of denial tends to fade on the third hospital day. Patients who manifest a post-MI depression may also be viewed as having suffered from an ego infarction (33). These fears, misconceptions, and injuries to

TABLE 1
Profile of Commonly Used Benzodiazepines

Drug	$t_{1/2}$ (hr)	Dose equivalent	Onset	Sedation
Oxazepam	5–15	15.0	Slow	+
Lorazepam	10–20	1.0	Intermediate	+ + +
Temazepam	9–12	10.0	Intermediate	+ +
Alprazolam	12–15	0.5	Intermediate	+
Diazepam	20–100	5.0	Fast	+ + +
Chlordiazepoxide	5–30	10.0	Intermediate	+ +
Clorazepate	30–200	7.5	Fast	+ +
Flurazepam	40–140	5.0	Fast	+ + +

one's self-esteem are important and need to be addressed. However, to qualify for a diagnosis of depression according to the DSM-III (34), one needs to manifest more than just a dysphoric or depressed mood. A neurovegetative symptom complex (with four or more symptoms for a duration of at least 2 weeks) is required to make the diagnosis. The symptoms of depression include:

1. a sleep disturbance (usually with early-morning awakening)
2. a decrease in interests and libido
3. the presence of guilt, or a preoccupation of thought
4. a decrease in energy
5. a decrease in concentration ability
6. a change in appetite (usually a decrease, but it may be an increase)
7. psychomotor agitation or retardation, and
8. suicidal thoughts, or thoughts of death.

The mnemonic SIG: E CAPS (that is, what you would think of when you wanted to write a "*pre-scription* for *e*nergy *caps*ules" to treat someone for a diagnosis of depression) provides a convenient method to recall the diagnostic criteria for depression.

Treatment. After the diagnosis of depression has been made, treatment should be initiated. This typically includes the combined use of either a traditional tricyclic or a newer tetracyclic antidepressant (collectively called polycyclic antidepressants) and psychotherapy.

However, before any of these agents are used, a number of issues need to be considered. The first question is, When is the best time to initiate treatment? Conservative practice dictates that treatment with polycyclic antidepressants should be avoided for the first 4–6 weeks following a MI. This is the time course for scar formation and healing of the injured myocardium. Moreover, during the initial phase of the MI, many patients are at increased risk for conduction disturbances, which might well be exacerbated by the quinidinelike effects of the polycyclic agents. In addition, because of the anticholinergic properties of the polycyclic antidepressants, tachycardia frequently accompanies treatment with these agents. This may place patients with ischemic myocardium at greater risk for the development of chest pain, congestive heart failure, and reinfarction. Another side effect of polycyclic antidepressant treatment is the development of orthostatic hypotension. This side effect has similar risks for the MI patient.

As a result of these cardiac side effects of polycyclic antidepressants, reviewed extensively elsewhere (35), most pharmacologic treatment of post-MI depression is postponed until several weeks following discharge. However, alprazolam, which has been reported to be both anxiolytic and antidepressant (36, 37), appears to be devoid of cardiac side effects. It therefore seems to be a suitable drug for the anxious and depressed cardiac patient. Results of a study on alprazolam's safety and efficacy in post-MI patients are currently pending (38).

The nonpharmacologic treatment of the acute phase of post-MI depression includes brief psychotherapy. Guidelines for this therapy are suggested in the following section on characterologic problems and have been reviewed in detail elsewhere (39). A major focus of this work is reassurance of the patient and introduction of cardiac rehabilitation. Since much of the concern that postinfarction patients describe is about fears of weakness and disability, early ambulation and entry into a rehabilitation program are essential to dispel these fears. Many hospitals have cardiac rehabilitation physical therapists who see patients even before their transfer out of the CCU.

Interpersonal Problems

Range, Timing, and Manifestations. Problems related to characterologic issues generally become manifest after the third hospital day (25). The most difficult of these problems for CCU staff are presented by demanding, regressed, or exhibitionistic patients. An even wider range of problems can be understood by placing the MI patient on a continuum of characterologic styles. Seven distinct personality styles have been identified, each of which has a characteristic reaction to illness. Management strategies have been devised to facilitate the hospital care of each of these types. It is important to remember two things: first, an individual need not demonstrate a pathologic degree of any of these styles, and second, an individual may manifest more than one of these traits.

Treatment of Characterologic Problems. Patients whose personality style is primarily the *hysterical* style tend to be dramatic and anxious and react to their illness as if it were an attack on their masculinity or femininity. They should be given support, reassured about their courage, and allowed to ventilate their fears. Detailed technologic explanations fail to diminish their anxiety and need not be provided.

The *obsessive* character tends to be meticulous, dull, and anxious. For this sort of patient, illness is a punishment for letting things get out of control. Providing the patient with detailed explanations tends to reinforce his or her sense of control and decrease anxiety.

Self-involved, narcissistic characters tend to view their illness as an attack on their sense of perfection and frequently manifest inappropriate anger toward staff. Support of their sense of self (self-regard) is necessary to avoid further decompensation.

One of the most annoying types for CCU nursing staffs is the *oral* character. Patients with this style tend to be demanding, clingy, and dependent and repeatedly call for assistance with the bedside call button. Support and firm limits on their boundless neediness are required to stave off fear of abandonment, which is exacerbated by their illness.

The *masochistic* character tends to display a long-suffering, depressed appearance. To these patients illness is a well-deserved punishment for their worthlessness. Reassurance about improvement often falls on deaf ears. A strategy that appreciates the patient's courage and ability to withstand suffering is readily accepted.

The *schizoidal* character is often remote, unsociable, and uninvolved. Illness is seen as an invasion of their privacy. To prevent an increase in anxiety, their desire for privacy and distance must be respected.

In *paranoid* personality style, individuals tend to be suspicious and accusatory and sense danger coming from outside themselves. Clear, simple, and often-repeated explanations are needed to clarify that they have an illness and to decrease their belief that they are being harmed by others.

Psychological Evaluation

Psychiatric consultation is frequently requested for patients in the CCU. In addition to the recognition and treatment of personality-style symptoms, diagnoses, and traits, the purpose of such consultation is often to provide the primary caregiver with added insight. By providing this information, the care of the patient may be facilitated. The patient's use of denial and an overall impression of how the patient views his or her condition are useful features of the psychological assessment of the MI patient.

Denial, a psychological defense commonly used by those in danger, may be protective to individuals who have suffered from a MI (40). However, if denial becomes too great (pathologic denial), it may interfere with the patient's acceptance of appropriate medical care. For example, if a 58-year-old man, 36 hr after his condition has been diagnosed as anterolateral MI, decides that he must go home to water his plants, he is probably manifesting poor judgment as a result of excessive denial. Attempts to uncover how a person coped with other dangerous situations in the past (military experiences, sporting events, injuries, for example) may provide a clue as to how a person will respond to the current illness.

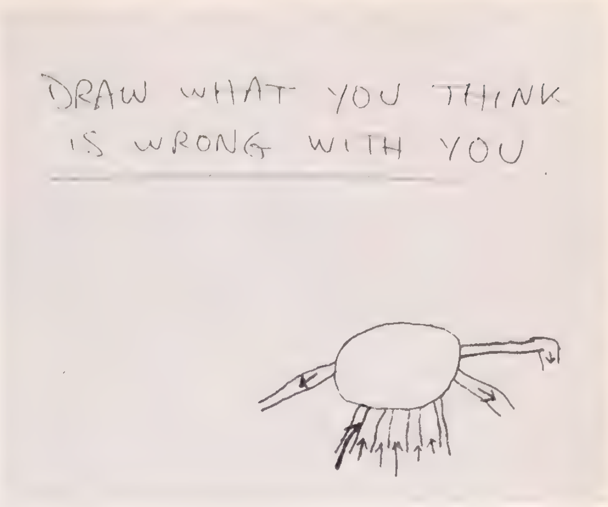

Fig. 2. Drawing by a 72-year-old plumber with an anterior wall myocardial infarction of what he thought was wrong with him.

Finding a common language with the patient makes the job of explaining the nature and consequences of MI easier. The use of metaphor can be seen in the following example. Mr. A, a 72-year-old plumber, sustained an anterior wall MI. While in the CCU he was asked to draw a picture of what he thought was wrong with him (Fig. 2). When asked to explain the picture he had drawn, he answered, "It's my heart. Blood is rushing in, making it pound. [It's] near the bursting point. There are not enough vents to let it out. [It] needs more outlets. [It] needs ventilation. You're the mechanic." Although his hypothesis was not physiologically accurate, it provided his physicians with a means of elaborating on an explanation of his condition which involved a discussion of flow rates, "clogged pipes," and methods of bypassing blocked areas.

Even to those uninitiated in the interpretation of psychological tests, the use of human figure drawings can be exceedingly useful in the generation of hypotheses about a patient's state of mind. Moreover, these tests are noninvasive, simple to administer at the bedside, and not time-consuming to interpret.

For example, a 38-year-old married man was seen in psychiatric consultation on his third day in the CCU. He had sustained a large anterior wall MI at the track, immediately after failing to place a bet on a race that would have paid him $6,000. On each of his first two nights in the CCU an individual was admitted to the bed opposite him and died of cardiogenic shock. Consultation was requested to assess and treat his anxiety.

As part of the evaluation he was asked to draw four pictures: draw a person, draw a person of the opposite sex, draw yourself, and draw what you think is wrong with you (Fig. 3). The impressionistic reactions of the CCU staff to these drawings included the following. The sketch of "a person" was notable for a sense of rigidity, with firm outlines of the upper body. The drawing of the person of the opposite sex showed a woman whom the patient described as "happy," but who seemed to be just the opposite. She was depicted as being large (not even fitting on the page) and muscular. The drawing of himself, seen in profile with his hand in his pocket, seemed sad and hopeless. The sketch of "what is wrong with you" was described by the patient as "being five views of myself, one tall, one short, one happy, one sad, and one in the middle—all headed toward the coffin."

The psychiatric interview confirmed his rigidity and need to be in control. It also revealed marital conflict; hostility was clearly evident. Most important, he sensed that he was about to die, like the two men in the bed opposite him. Anxiolytics were prescribed, reassurance about his medical status was provided, and brief psychotherapy directed toward his need for control was initiated. He survived his hospitalization and continued in outpatient psychotherapy following discharge.

Another individual, a 40-year-old pharmaceutical salesman, was admitted to the CCU following an acute MI. On the second day in the unit he was asked to draw the same four human figures. His drawing of "a person" (Fig. 4) is smiling and standing as if on tiptoes. His representation of what he thought was wrong with him is shown with a broken heart and without hands. Clinically his sense of denial was wearing thin, and he felt hopeless (in a fashion consistent with his handless figure).

Ten days later, still in the hospital, he was being prepared both medically and psychologically for coronary artery bypass grafting. He was asked to draw the same figures again. This time his image of a person (Fig. 4) was shown with his feet firmly on the ground, working in the garden (possibly on cabbages). In addition, buttons are clearly evident on his shirt (possibly symbolizing the upcoming suture lines that would be present postsurgery). However, despite this optimistic view, his drawing of "what is wrong with you" revealed a sad figure, hands by his side, with a broken heart, displaced laterally (as if he was contemplating the results of cardiac surgery). He died in the operating room.

Delirium

Range, Timing, and Manifestation. According to the DSM-III (34), the hallmarks of delirium are a clouded consciousness, disorientation, memory impairments, perceptual disturbances such as illusions or hallucinations, incoherent speech, an increase or decrease in psychomotor activity, and a disturbance of the sleep-wake cycle. The clinical features of the syndrome characteristically fluctuate over the course of a day. Delirium commonly develops in seriously ill patients and can arise at any point during a patient's stay in the intensive-care or cardiac-care unit (25). In past years patients who manifested the symptoms of delirium were frequently diagnosed as suffering from "ICU psychosis." To many this implied a nonmedical, psychosocial etiology ("the patient became confused because of the unfamiliarity of the hospital environment"). The treatment of patients with potentially life-threatening conditions was often limited to nonpharmacological modes.

Indeed, over the last decade a wide range of clinical conditions, metabolic states, and medications have been identified as potential precipitants of delirium (41–43). Postinfarction patients are at risk for the development of delirium by virtue of their tenuous clinical status and of the pharmacologic agents they receive. Factors that commonly result in delirium in this population include hypotension, central nervous system toxicity of antiarrhythmic agents, hypoxia, electrolyte imbalance, and anticholinergic excess (from atropine, for example).

Treatment. Essential to the management of the delirious patient is the identification of the etiologic agent. If the delirium is secondary to an adverse reaction to a medication, the offending agent must be withdrawn and a specific antidote administered if such an antidote exists. While the search for the precipitating factor proceeds, a combination of common-sense psychosocial, orienting activities is provided, and neuroleptic

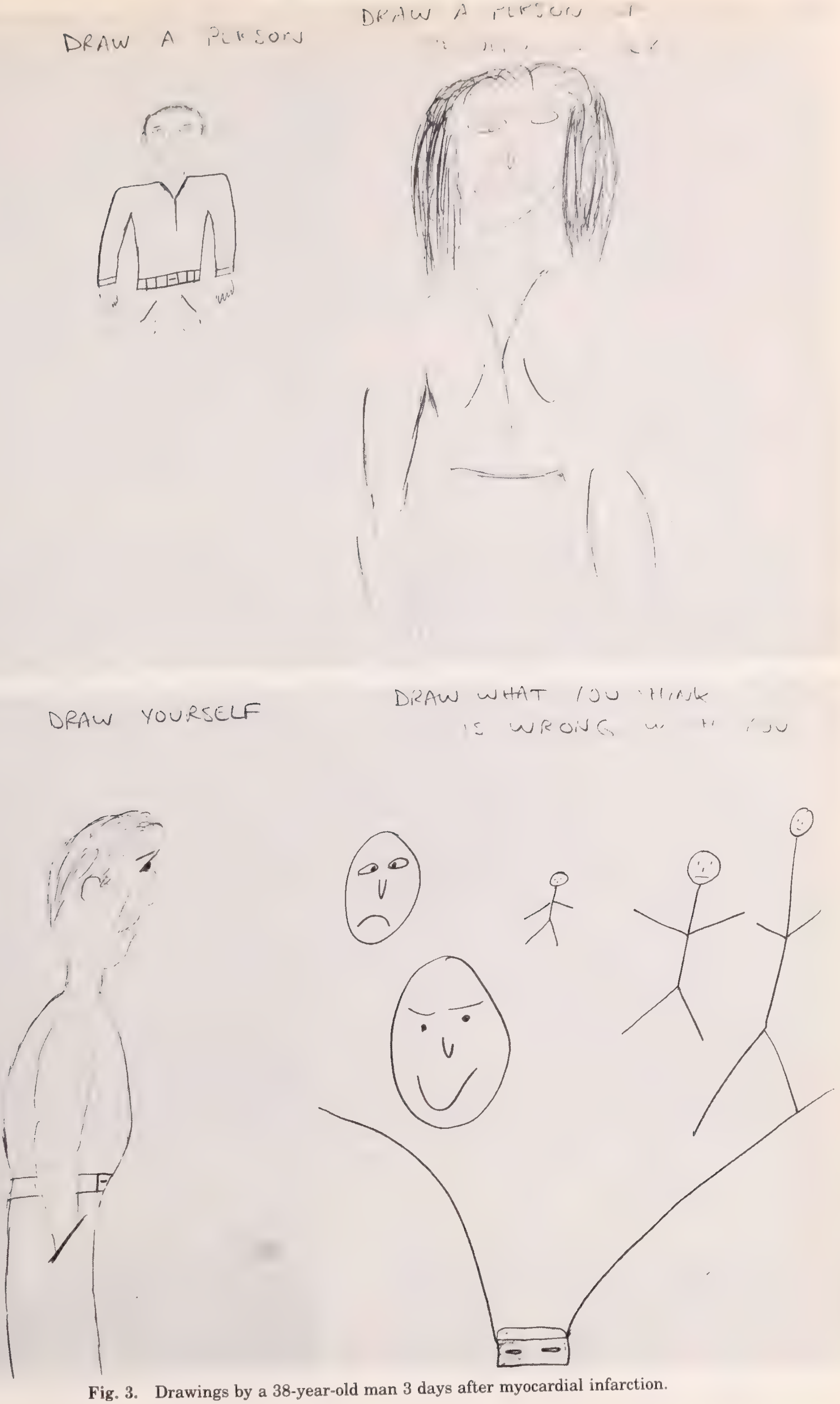
DRAW A PERSON
DRAW A PERSON OF
DRAW YOURSELF
DRAW WHAT YOU THINK IS WRONG WITH YOU

Fig. 3. Drawings by a 38-year-old man 3 days after myocardial infarction.

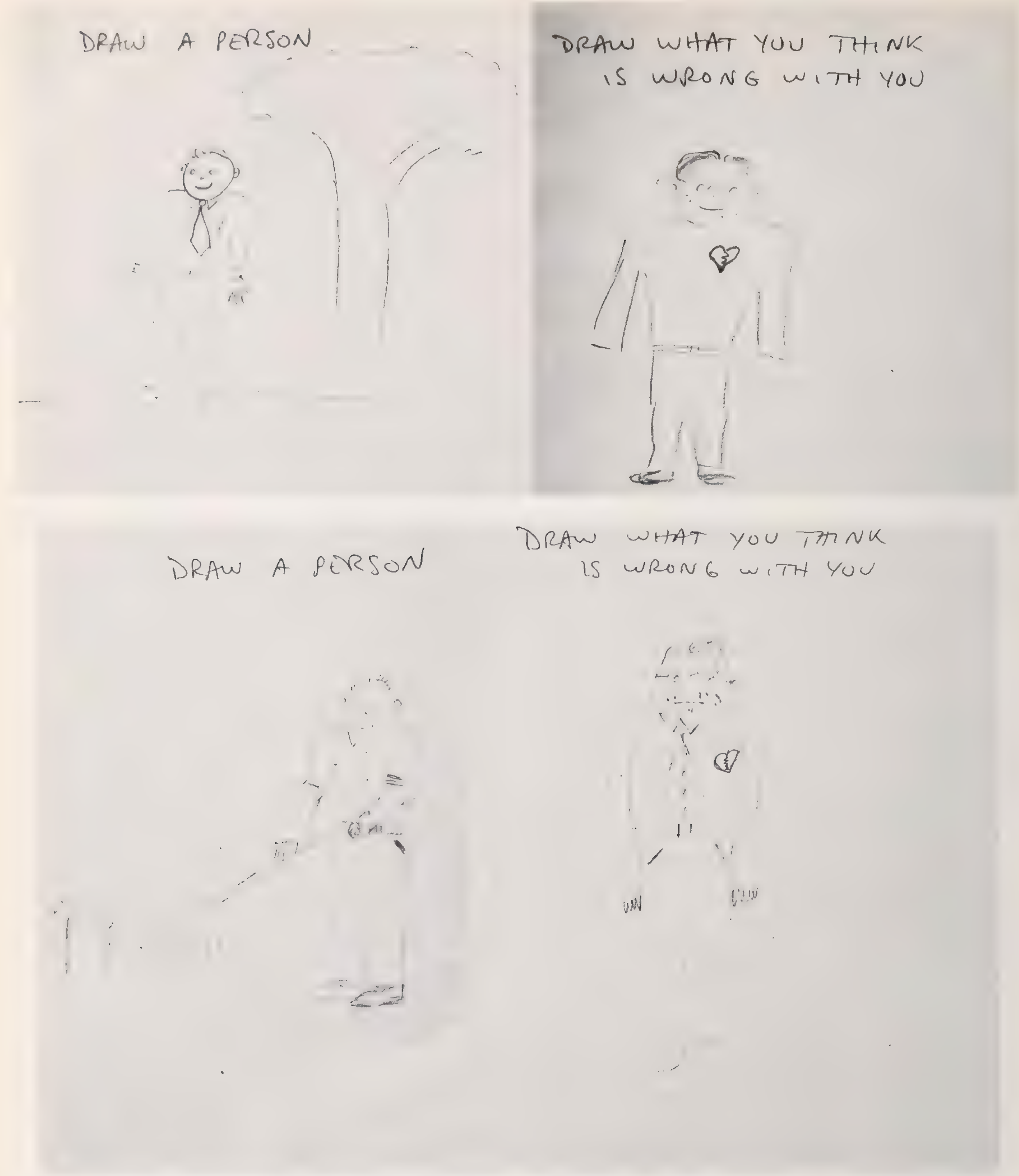
DRAW A PERSON
DRAW WHAT YOU THINK IS WRONG WITH YOU
DRAW A PERSON
DRAW WHAT YOU THINK IS WRONG WITH YOU

Fig. 4. **Above** Drawings by a 40-year-old man two days after myocardial infarction. **Below** Drawings by the same 40-year-old man 12 days after the infarction.

medication is administered. Control of an agitated patient's behavior is essential to protect the patient from self-harm (pulling out the pulmonary artery catheter, for example).

At the Massachusetts General Hospital the neuroleptic agent most commonly used in the CCU to control agitation and confusion is intravenous (IV) haloperidol (44). It is a rapidly acting (half-life, rapid phase, 3–19 min; $\bar{x}$, 11 min), potent neuroleptic agent (approximately 50 times as potent as chlorpromazine, milligram for milligram). It has been shown to be noncaustic to veins and safe with respect to its effects on blood pressure, heart rate, and respiratory rate (45). When

IV haloperidol is being used, it is important to bear in mind that when hypotension does occur, it tends to result from hypovolemia. If a pressor agent is required, alpha agents should be used and epinephrine should be avoided. Since IV haloperidol has been shown to precipitate with solutions of phenytoin and heparin (46), the IV line must be flushed with 5 ml of saline before haloperidol is given, if these medications are present.

Doses begin at 2 mg for mildly agitated states, at 5 mg for moderately agitated states, and at 10 mg IV for severely agitated states. Doses are given (and doubled) every 15–20 min until the target symptom is successfully treated. After calm is achieved, repeat doses are given when symptoms recur. The largest single IV bolus used at the MGH to date has been 150 mg, and the highest cumulative, 24-hour IV dose has been 975 mg.

The use of this method of rapid neuroleptization typically allows patients to avoid the endotracheal intubation which might be required if more sedating agents, such as narcotics (morphine) or benzodiazepines (diazepam), are employed.

Transfer to the Step-Down Unit

Although transfer from the CCU to the step-down unit is clearly a sign of improvement and progress, it is often accompanied by problems. Some patients become anxious because they no longer have the intensive observation of an ever-present nursing staff and sophisticated cardiac monitoring system. In one study (47) this tension was found to result in an increase of 24-hr urinary catecholamine production and was associated with an increased incidence of periinfarction complications. When a similar group of postinfarction patients was guided through the transition to the step-down unit by introduction to the routines and personnel of the step-down unit, urinary catecholamines remained normal, and there was an absence of periinfarction complications. Prior to transfer, every effort should be made to inform the patient of the upcoming move and to place the transfer in the context of the patient's improvement and lack of need for continuous monitoring and care.

Sleep patterns, which were disrupted by the MI and by the stay in the CCU, take a number of days to normalize. During this phase of treatment, the use of sedating agents will help ensure that the patient gets the rest necessary for continued improvement.

Adequate preparation for discharge is also essential. Attention should be given to making sure the patient understands the nature and proper timing of prescribed medications. In addition, explicit directions should be given to the patient and to his or her spouse on the amount and timing of exercise and sexual activity permitted. Follow-up appointments should be given, and contact with a cardiac rehabilitation program should be encouraged. Each of these steps will help to allay the anxiety that frequently accompanies hospital discharge.

Posthospital Course

After discharge from the hospital, postinfarction patients are still susceptible to anxiety and depression (48). The treatment of these problems is an extension of the treatment initiated during the hospital stay.

Anxiety. Anxiety can best be managed first by identifying the nature and extent of the problem and then by beginning an appropriate course of therapy. Reassurance, explanations, and enrollment in a cardiac rehabilitation program are useful steps in this process. In addition, the ongoing use of benzodiazepines can help reduce excess anxiety. Further benefit can be achieved by the patient's enrollment in a group for postinfarction patients to provide both support and education (17, 18, 49). For selected patients, individual psychotherapy may also be indicated to help manage and resolve the conflicts that are contributing to their distress.

Depression. After a number of weeks have passed, it becomes reasonable to consider the treatment of depression with traditional antidepressants. The determination of which antidepressant to use (Table 2) is made by looking at several issues (35).

1. Is a sedating or a stimulating agent required? If sedation is desired, then doxepin or

TABLE 2

Profile of Commonly Used Antidepressants

Drug	Biogenic amine affected		Hypotensive properties	Anticholinergic potencies
	5-HT	NE		
Doxepin	+ + +	0	+ + +	+ +
Amitriptyline	+ + +	0	+ + + +	+ + + + + + +
Imipramine	+ + +	+ +	+ + + +	+ +
Nortriptyline	+ +	+ +	+ +	+ +
Desipramine	0	+ + + +	+	+
Protriptyline	0	+ + + +	+	+
Trazodone	+ + +	0	+ + +	0
Alprazolam	0	0	0	0

amitriptyline is appropriate. If stimulation is required to treat a retarded depression, then desipramine or protriptyline is indicated.

2. Is there a history of a prior positive response by the patient, or a relative, to a particular antidepressant? If there is, it is more likely that the individual will respond to that same agent.

3. Can the patient tolerate the side effects of the treatment? The most important of these are orthostatic hypotension (which tends to occur before the therapeutic effect of these agents), anticholinergic effects (including tachycardia and a dry mouth, which often leads to an increase in fluid intake), and effects on the conduction system. These effects are similar to those produced by quinidine and other group I antiarrhythmics and include the prolongation of atrial and ventricular depolarization (mostly in the His-ventricular portion of the conduction system), increases in the duration of the P-R interval, widening of the QRS complex, and lengthening of the QTc (with the risk of sudden death in association with a QTc length greater than 440 msec).

Effects on the Family. Since the patient is not the only victim of the MI, family evaluations may also prove useful. It has long been recognized that the spouse of the MI patient is often subject to a host of uncertainties, concerns, and fears (50): How much can my spouse do? Is it safe to perform sexually? When can he or she return to work? How much tension in the household can he or she tolerate? It is important to realize that adolescent children are also subject to difficulties. Wishnie et al (51) noted that adolescent children responded to parental MI with a more extreme emotional reaction (depression, guilt, a decline in academic performance, drug abuse) than either older or younger children. Once these problems are identified, the child can be referred to the appropriate treatment resources.

The cornerstone of the successful management of the postinfarction patient is cardiac rehabilitation (52). Anything that can be done to encourage the patient to improve habits, life-style, and physical condition will prove to be mentally and physically useful (53).

Summary

Recognition and management of the symptoms of anxiety and depression are tasks that begin with a patient's arrival in the hospital and continue during and after hospitalization. Diligent treatment with anxiolytics, antidepressants, and nonpharmacologic interventions (group support, reassurance, education, and cardiac rehabilitation) can facilitate improvement and decrease future morbidity.

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Noncardiac Surgery in the Elderly Patient with Heart Disease

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Advances in the conduct of surgery over the last thirty years have been noteworthy. Newer anesthetic agents have a less depressant effect on the heart and other major organ systems. It is now possible to offer specific pharmacologic intervention in a variety of critical clinical situations. Cardiac function can be assessed throughout a surgical procedure. Blood and fluid volume and pH and chemical equilibrium can be measured precisely. Because of these advances, surgery in elderly patients with or without cardiac disease, known or unsuspected, can now be undertaken with more confidence. Elective as well as emergency procedures are increasingly performed; the approach to surgical correction of abdominal aortic aneurysm is only one example.

However, the ability to identify disease states preoperatively and to offer specific support for a great number of clinical problems does not permit a casual approach to the assessment of surgical risk. A significant mortality is associated with surgery under both general and regional anesthesia (5.9% in one large series) (1). Classification of potential surgical risk is useful in the same way that the classic Framingham studies have been helpful in identifying risk factors for the development of heart disease. Analysis of multiple risk factors adds to the precision of such prediction.

The wide use of potent therapeutic agents in medicine causes additional problems. For example, the use of digitalis by older patients with reduced renal function, the use of beta-blocking agents and the timing of their withdrawal if necessary, the use of antihypertensive agents, inotropic agents, vasodilators, and antiarrhythmic agents must all be carefully weighed. A meticulous history of sensitivity reactions is essential. Special attention must be directed to patients with myocardial infarction (old or recent), those who have had coronary bypass surgery or valve replacement, and those on chronic anticoagulation.

Current review of this subject is indicated for several reasons. We have pertinent information obtained from physiologic studies of the older patient (for example, the data presented in 1981 at the Fourth Kingsbrook Conference by Dr. Roger Hickler, of the University of Massachusetts, on the metabolism of cardiac drugs and their clinical implications). Experience is increasing in the use of anesthesia in patients undergoing coronary bypass surgery and in patients with general surgical problems after coronary bypass. The effect of new drugs, such as calcium channel blockers, needs to be reviewed; at this time we do not have enough data on their effects in surgical patients. A plan for postoperative studies to identify intraoperative and perioperative problems merits attention. Finally, our current screening procedures warrant critical review for their usefulness in management. Cost containment should not lead us to cutting corners on patient care. We should consider the possible impact of ambulatory surgery.

Determination of Risk Factors

The evaluation of risk in older patients for whom surgery is planned has been of considerable interest to anesthesiologists, physicians, and surgeons. Currently the most widely used classification is that of Dripps (2, 3), which has been accepted by the American Society of Anesthesiologists and the American Surgical Association.

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This scheme has been useful, but it is relatively subjective and general, takes no account of perioperative events, and is based on studies completed 25 years ago.

In 1977 (4) and 1978 (1) Goldman and his coworkers presented a detailed analysis of cardiac risk factors in patients over 40 who were operated on by the ward services of general, orthopedic, or urologic surgery or by cooperating private surgeons at the Massachusetts General Hospital between October 1975 and April 1976. A total of 1,001 patients over 40 were included. Patients undergoing minor procedures under local anesthesia, uncomplicated endoscopies, or transurethral resection of the prostate were excluded—those in the first two categories because of the limited nature of the procedure, and those in the latter because the authors felt there was sufficient evidence of the safety of the procedure even in elderly patients with heart disease. Of the 1,001 patients, 19 died postoperatively of cardiac causes, 40 died of noncardiac causes; 39 had one or more life-threatening cardiac complications but did not die of cardiac causes. Intraoperative or postoperative myocardial infarctions occurred in 18 patients, pulmonary edema in 36, and ventricular tachycardia in 12.

Multivariate analysis of these patients identified nine factors with statistically significant independent correlations with cardiac outcome. The authors also performed univariate analysis of the independent risk variable and the development of cardiac complications. By use of a discriminant function coefficient assigned to each statistically significant factor, a "point" value for the factor was derived. Four risk categories were defined from computation of each patient's point total.

The number of life-threatening cardiac complications and cardiac deaths was least in Class I (0–5 points) and greatest in Class IV (26–53 points). Class II (6–12 points) and Class III (13–25 points) had similar risks for cardiac deaths, and both groups had statistically significant higher risks of cardiac death than Class I. Class IV was a group of 18 patients at especially high risk, 10 of whom died from cardiac causes. The Goldman cardiac risk index was superior to the Dripps–American Surgical Association index in the identification of the 18 patients at especially high risk.

The factors of clinical importance determined by Goldman's group, in order of statistical significance, were

- S 3 gallop or jugular vein distention on preoperative examination
- myocardial infarction in the preceding 6 months
- rhythm other than sinus or premature atrial systoles on preoperative electrocardiograms
- more than five ventricular premature systoles per minute documented at any time before operation
- procedures involving the abdominal or chest cavities or the aorta
- age of 70
- "important" valvular aortic stenosis
- emergency operation
- poor general medical condition (hypoxia, hypercarbia, hypopotassemia, elevation of blood urea nitrogen or creatinine, elevated transaminase, evidence of chronic liver disease or patient confined to bed for noncardiac causes)

This work is of obvious importance in directing our attention to specific areas that should be carefully reviewed before operation. It is striking that every one of these factors of significance can be determined from the careful history, physical examination, and basic electrocardiographic studies that good practice dictates prior to surgery. Advanced technology is not required. What is required is care, and I have used the modifier "careful" to emphasize the type of preoperative assessment required. A number of committees of examining boards in various specialties have noted and criticized the decline in the basic skills of history taking, physical examination, and synthesis of findings from them in candidates for board certification in recent years.

This injunction to obtain a complete history and to perform a careful physical examination and laboratory evaluation may seem akin to reinventing the wheel. In his work on vaccination against pneumococcal pneumonia, Dr. Robert Austrian has shown us that at times such rediscovery is most useful. Twenty-six years of experience in cardiology have convinced me that a major shortcoming in patient care is the failure to obtain pertinent information on the patient's history from the patient or the patient's family, from physicians who have previously cared for the patient, and from available medical and hospital records. Related to this is the practice of not allowing sufficient time for adequate physical examination. I believe this is often the case in teaching hospitals where the services of resident physicians are available. It is not acceptable to substitute the findings of a resident, no matter how capable, for your own evaluation. Further, it is clear that reading a report is not an adequate substitute for personal review of pertinent X-ray films with a radiologist who then functions as a true consultant. Equally important is personal contact with the anesthesiologist. The utility of this collaboration has been demonstrated by Wells and Kaplan (5) in a review of their experience at Emory University with patients with ischemic heart disease undergoing noncardiac surgery.

Anesthetic Agents. As with other pharmacologic agents, any agent capable of producing effective anesthesia carries the risk of undesired effects. These include a depressant effect on cardiac contractility and the cardiac conduction system and changes in autonomic tone and circulating catecholamine levels which affect preload and afterload and, through this mechanism, cardiac output. The agents in common use today are not as likely to cause nausea and vomiting as in the past. Combined use of a general anesthetic with muscle relaxants permits desired levels of anesthesia without profound central nervous system depression. It is agreed that the care with which the chosen agents and techniques are employed is more important than the specific anesthetic chosen. Careful monitoring of arterial pressure and respiratory status is critical. Unanticipated reduction of systolic pressure of 33⅓% for longer than 10 min has been shown to be correlated with a fivefold increase in incidence of death from cardiac causes (1).

I offer a brief discussion of some anesthetic agents to illustrate the problems they pose and the choices that must be made.

Halothane causes myocardial depression which is dose dependent. A combination of enflurane, 40% nitrous oxide, and a muscle relaxant such as pancuronium causes less myocardial depression.

Especially during induction, disorders of rhythm are common and may usually be managed by attention to anesthetic technique. Thiopental is a particularly useful choice for induction in patients with a history of arrhythmia. It does cause some myocardial depression and vasodilatation and is therefore poorly tolerated by patients with fixed cardiac output and secondary vasoconstriction. Ketamine is an attractive alternative to thiopental in certain circumstances. It has a cocainelike action, preventing uptake of catecholamines at postganglionic sympathetic terminals with mild sympathetic stimulation. It is a desirable choice in patients with congenital heart disease, allowing a high concentration without causing hypotension in the usual dose range. It is relatively contraindicated in patients with increased blood pressure or significant mitral stenosis who may tolerate tachycardia poorly.

Diazepam is used frequently in premedication and as an induction agent. Its effect is dose related: low doses have little effect on cardiac function, but larger doses may reduce stroke volume by one-third. Arrhythmias are also likely to occur during intubation, eye manipulation, and traction on viscera. Control of myocardial oxygen demand during operation is important; nitroglycerine and nitroprusside can accomplish this. Propranolol is useful as well—its action in decreasing myocardial oxygen demand usually counteracts its negative inotropic action.

Spinal, epidural, regional, and local anesthesia are alternatives to general anesthesia. The lower mortality attributed to the selection of such modes of anesthesia is related to the type of surgery in which they are employed, usually less extensive surgery and rarely involving the thoracic or abdominal cavities. General anesthesia causes myocardial depression and lowers the threshold for arrhythmias. Balancing this is the marked hypotension that may be produced by sympathetic blockade, particularly in the patient with hypovolemia (6).

Type of Operation. The risk of surgery is related to the nature of the operation. There is a greater mortality for all patients with operations involving the body cavities or major vascular surgery. For patients with heart disease the risk of mortality with cholecystectomy, subtotal gastrectomy, or bowel resection is twice that of patients with no heart disease. There is a lower and equal mortality for hernia repair or transurethral prostatic resection. (7).

Emergency operation is associated with a much higher risk of mortality. For cholecystectomy as an emergency, the mortality is 29%, against 10% for the same surgery electively. For emergency bowel resection, the mortality is 50%, against 18% as an elective procedure. Other intraperitoneal procedures have a 47% mortality when performed as an emergency, against 21% as an elective. Goldman and his associates found a four times greater likelihood of postoperative infarction or cardiac death in patients over 40 who had emergency major surgery (1) than in those who had elective surgery.

Length of Operation. There is no clear relation between the duration of anesthesia and the risk of cardiovascular morbidity and mortality. Skinner and Pearce (7) found an inverse relation between mortality and duration. Tarhan and his associates (8) reported an increased incidence of reinfarction with increasing time under anesthesia. Steen and associates found that in surgery involving the aorta, thorax, and upper abdomen in patients with previous myocardial infarction, mortality was directly related to the duration of anesthesia (9). Goldman and his colleagues noted an increased risk of heart failure, but not of reinfarction or cardiac death, when surgery lasted more than 5 hr (1). Intuition, which is not a reliable guide, supports the concept that longer is not better with anesthesia.

Age. This symposium is directed to the care of the elderly patient. Recent studies on the relation of age to the risk of surgical morbidity and mortality suggest a small, but progressive, increase with age. Goldman found that age over 70 was one of the significant factors in the development of postoperative life-threatening or fatal cardiac complications (4). In their recent excellent work on medical consultation, Gross and Kammerer state that the age at which the risk of surgery is significantly increased, which 40 years ago was judged to be at 50–60 years, is at present judged to be at 65–80 years. They give a range from 0.9% mortality for all operations in patients aged under 65 to 5% for patients over 65 years (10).

A number of current reports indicate mortality from anesthetics and surgery of 1%–2% for patients aged under 60 years and 5%–15% for patients above age 65. Over age 80 the risk is 10%–20% (10). As in all age groups, the risk is related to the type of operation and whether it is an emergency or an elective procedure. Age-associated physiologic changes, such as decreased blood flow to the brain, heart, and gut, which have been determined with precision in recent years, explain these results.

Congestive Heart Failure. The importance of congestive heart failure was emphasized by Goldman and his associates, who found an S 3 gallop or jugular vein distention to be the most significant risk factor in the development of postoperative life-threatening or fatal cardiac complications. Either of these findings was assigned 11 points (the highest possible number of points being 53) in their cardiac risk index. In Goldman's Massachusetts General Hospital series, 6.3% developed new or worse congestive heart failure and 3.6% developed pulmonary edema from cardiac causes. The mortality in this series for those developing pulmonary edema was 57%. Patients who did not progress to overt pulmonary edema did not have a higher mortality from cardiac causes, but had a 15% mortality from other causes (4). These findings are consistent with those reported by Skinner and Pearce in 1964. They showed a correlation between the New York Heart Association classification and the mortality from major noncardiac surgery (I—4%, II—11%, III—24%, IV—67%) (7).

It is clear that the presence or potential for development of congestive heart failure must be carefully considered, and that treatment should begin prior to major elective noncardiac surgery. Delay of scheduled surgery to achieve control of congestive heart failure is indicated. The hazard of fluid overload should be considered, and records of intake and output and weight should be reviewed. Myocardial infarction may be the cause of pulmonary edema in the patient with heart disease and diminished reserve. Measurement of the pulmonary capillary and pulmonary artery pressures may be helpful. Much as in younger patients, management is accomplished with diuretics, oxygen, morphine, afterload reducers, and inotropic agents (e.g. digitalis) as required. Risks of treatment include dehydration, hypovolemia, and hypokalemia. The periods of greatest risk for the development of pulmonary edema occur intraoperatively or immediately postoperatively. Cooperman and Price found 75% of cases developed within 30 min and 95% within 60 min of the end of the operation (11).

There is no agreement, despite much discussion, as to the value of prophylactic digitalization for congestive heart failure. The advocates of digitalis used prophylactically cite the benefits of protection against supraventricular arrhythmias and control of ventricular rate if they develop. Its opponents note that digitalis may cause perioperative dysrhythmias, that it adds to the hazard of electrical cardioversion, that the appropriate dose of digitalis is difficult to determine in the absence of arrhythmia or failure, and that proof of benefit is lacking.

I do not favor truly prophylactic digitalization. If needed, it can be given with dispatch, by vein if required. Wolf and Braunwald recommend digitalization if there is a history of heart failure without subsequent corrective cardiac surgery, in patients with a history of recurrent supraventricular tachycardia, in patients with moderate or severe valvular disease, and in elderly patients who are to have pneumonectomy even without known heart disease (6).

Ischemic Heart Disease. Patients with coronary artery disease are at much greater risk during major noncardiac surgery than patients without heart disease. Large series have yielded similar findings. Knorring studied 12,654 patients having major surgery under general or regional anesthesia from 1975 to 1977 (12). There were 12 myocardial infarctions in patients with no previous evidence of heart disease (0.1%). Of 214 patients with preoperative myocardial infarction or electrocardiographic evidence of left ventricular hypertrophy or subendocardial injury, 38 had postoperative myocardial infarctions (17.7%); 18 were transmural and 17 subendocardial by electrocardiographic criteria, and in three others transmural infarction was diagnosed at postmortem examination. Excluding 3 fatal cardiac arrests, 13 of the total of 38 postoperative infarctions occurred without clinical symptoms, the diagnosis being made by serial electrocardiograms.

Earlier studies have been consistent with the Helsinki findings. In 1964 Topkins and Artusio reviewed the New York Hospital experience between 1959 and 1963 (13). They included 35,937 patients in their initial evaluation. A total of 12,712 male surgical patients over 50 were selected for further study because preliminary results showed that 80% of all surgical patients suffering myocardial infarction were in this group. Of 12,504 patients with no prior history of infarction, 79 had a postoperative myocardial infarction—an incidence of 0.66%. Of 658 patients with preoperative infarction, 43 sustained a postoperative infarction—an incidence of 6.5%. The mortality rate of a first infarction was 26.5%, compared with 70% for a second infarction. Topkins and Artusio found that the rate of reinfarction was highest when the interval between infarction and subsequent surgery was less than 2 years.

Also in 1964, Arkins, Smessaert, and Hicks reported on a study of 1,005 consecutive surgical patients with diagnosed coronary artery disease operated on at St. Vincent's Hospital, New York City. The mortality rate was 22.3%, twice that of similar patients without ischemic heart disease. In 605 patients over 70 years of age who were not diagnosed as having coronary artery disease, the mortality rate was 10.8%. Patients with a poorer Dripps–American Surgical Association rating had a higher mortality, as did those undergoing emergency (45.2%) compared to elective (18.3%) surgery. Of 240 patients who had had myocardial infarction more than 3 months prior to surgery, 54 died (22.6% mortality). In 27 patients who had had infarction less than 3 months before surgery, there were 11 deaths (40%), 10 from cardiac causes. The outcome was worse with transmural than subendocardial infarction; 55 patients who had had transmural infarction had a postoperative myocardial infarction, with 69% mortality.

In 1972 Tarhan et al reported the Mayo Clinic experience with 32,817 patients who had general anesthesia in 1967 and 1968 (8). Forty-three patients without previous infarction had a postoperative myocardial infarction (0.13%); 28 of 422 (6.6%) patients with prior infarction had a second infarction within the first week after operation. These figures are quite similar to those of Topkins and Artusio. Patients operated on within 3 months of infarction had a 37% reinfarction rate. This decreased to 16% if the operation was performed 3–6 months after infarction and 4–5% when infarction had occurred more than 6 months prior to surgery.

Steen, Tinker, and Tarhan reported from the same institution the 1974–1975 experience with 587 patients who had a prior myocardial infarction (9). Thirty-six (6.1%) had a reinfarction, and 25 of these (69%) died. Patients operated on within 3 months of the previous infarction had a 27% reinfarction rate. This fell to 11% if the infarction occurred 3–6 months before surgery and to 4–5% if the interval had been more than 6 months. These findings were quite consistent with the series cited previously.

The New York Hospital, St. Vincent's, and first Mayo studies were in agreement that the outcome was not related to the anesthetic agent, the type of operation, or the duration of anesthesia and surgery. Steen's later Mayo study identified as specific risk factors preoperative hypertension, hypotensive episodes during surgery, and thoracic or upper abdominal operations of more than 3 hours' duration. These workers found a striking correlation with reinfarction and the time under anesthesia. The finding that the type of surgery (thoracic, upper abdominal) affects the outcome anticipated and is consistent with the findings of Goldman and his associates.

No statistically significant improvement occurred in the incidence or mortality of perioperative myocardial infarctions between two groups of patients operated on 8 years apart at the same excellent institution. The improvement anticipated from advances in monitoring, newer anesthetics, and other pharmacologic agents was not demonstrated. Two recent series have reported a much lower incidence of perioperative myocardial infarction. Wells and Kaplan reviewed 48 patients who had noncardiac surgery 3 months after infarction with no reinfarctions; 15% had significant disorders of rhythm (5). Rao and El-Etr (15) reviewed 38 patients operated on within 3 months of infarction with a 7.8% incidence of reinfarction, and 59 patients operated on 3–6 months postinfarction with a reinfarction rate of 3.4%. For both groups, extensive intraoperative monitoring was employed. Weeks and Kaplan emphasized close cooperation between anesthesiologist and cardiologist as vital to success.

These encouraging results do not furnish sufficient evidence to permit any relaxation of efforts to increase the safety of surgery in older patients with heart disease. Further studies incorporating the effects of coronary bypass surgery and involving a larger number of patients are required. The relative contraindication to elective surgery within 6 months of a myocardial infarction still seems sound practice.

An important feature of perioperative myocardial infarction is the frequent absence of clinical symptoms. Less than 50% of the patients studied at the Massachusetts General Hospital and the Mayo Clinic had chest discomfort with their infarctions (1, 9). Serial electrocardiograms and biochemical determinations (MB fraction of serum creatine kinase) are necessary for accurate diagnosis.

Effect of Coronary Bypass Surgery. Since 1968 between 750,000 and 1,000,000 coronary artery bypass grafts have been performed in the United States. There have been technical improvements in the procedure and in protection of the myocardium during surgery. Morbidity and mortality have been reduced over this period. The indications and long-term results of this surgery are under continuing review (National Heart, Lung, and Blood Institute Cooperative Coronary Artery Surgery Study).

A 1978 report from the Methodist Hospital, Houston suggests that successful revascularization of the myocardium may reduce the risk of noncardiac surgery in patients with ischemic heart disease (16). Crawford and his colleagues studied 358 patients who had had coronary bypass and then required noncardiac surgery. Only patients who had both the coronary artery surgery and the noncardiac operations at the Methodist Hospital were included to assure adequate analysis. A total of 266 patients (74%) had one operation, 70 (20%) had two, and 22 (6%) had three or more. The operations included aortic, vascular, thoracic, and general surgical procedures, including resection of abdominal and thoracic aneurysms, carotid endarterectomy, femoral artery bypass grafting, lung and esophageal resection, cholecystectomy, and bowel resection. Seventy patients had operations planned before the coronary surgery and carried out between 6 weeks and 3 months after bypass. (The remaining operations were for new or previously unrecognized conditions and were performed from 10 days to 89 months after bypass.) There were 4 perioperative deaths (1.1%) in these 358 patients. Two were from cerebrovascular accidents, one from dissecting aneurysm of the ascending aorta, and one from gangrene of the abdominal wall following splenectomy for hypersplenism associated with chronic leukemia. Three perioperative deaths and a higher percentage of complications occurred in patients brought to surgery within 30 days of the coronary bypass. In 12 patients (3%) late death was due to myocardial infarction.

A smaller series (60 patients) who had coronary bypass surgery prior to major noncardiac surgery was reported from the same department one year earlier (17). These 60 patients had 77 major procedures with no perioperative mortality and no myocardial infarction.

In 1976 Scher and Tice reviewed 20 patients who had major noncardiac surgery following coronary bypass grafting (18). Twelve had elective and four had emergency procedures from 3 months to 5 years following the myocardial revascularization. There were no deaths in the elective group. One of four patients in the emergency series died from sepsis following splenectomy for splenic abscess.

These results are clearly better than those cited previously for noncardiac surgery in patients with ischemic heart disease (12–14). Further studies are required, but these are encouraging.

Hypertension. Hypertension alone is not a major risk factor in noncardiac surgery (1). Its importance is in its severity and duration, which may lead to coronary or cerebrovascular insufficiency, congestive heart failure, or renal insufficiency. As a rule, only emergency surgery should be undertaken in patients with evidence of significant impairment of circulation to the brain, heart, or kidneys.

It is wise to control blood pressure elevation prior to elective surgery, but not to hurry this control because of the risks of alkalosis, hypokalemia, and volume depletion. Hypokalemia can be accentuated by intraopertive hyperventilation. These are potential problems in all patients being treated with diuretics.

A good deal of experience has been obtained with a number of antihypertensive agents. The hazards of diuretics have been cited above. Earlier concern about the use of β blockers has been relieved. Experience with coronary bypass surgery has been helpful. In a well-designed prospective study, Wechsler showed that propranolol should be maintained until operation for its beneficial perioperative effects in reducing myocardial oxygen consumption and as an antiarrhythmic agent (19). Its negative inotropic effect can be counteracted if necessary. Stephenson's study supported the use of propranolol against arrhythmias. Certain antihypertensive agents deserve special consideration. MAO inhibitors should be discontinued at least 2 weeks prior to surgery because of the potential for serious drug interactions. The use of clonidine should be gradually reduced prior to surgery, to prevent withdrawal syndrome. The concern about maintenance of blood pressure in the face of significant blood loss for patients taking the converting enzyme inhibitor captopril has not been supported by experience. Hypotension is corrected readily by volume expansion. There is not sufficient experience with the calcium channel blockers to make definitive recommendations concerning them.

Monitoring is important in patients with hypertension, even when the condition is controlled. They are subject to marked variations in blood pressure—both elevation and drops—which require management. Intraoperative hypotension is a major risk factor for cardiac mortality (1). Induction and intubation are periods when significant blood pressure elevation is likely. Postoperative hypertension may follow reconstructive carotid surgery or repair of an abdominal aortic aneurysm. The mechanism has not been established.

Control of mild hypertension may be quite important in brain, retinal, or plastic surgery to prevent hematomas.

Valvular Heart Disease. There is limited information on older patients with valve disease undergoing noncardiac surgery. Goldman and his colleagues identified "important aortic stenosis" as a significant risk factor (4). There is an impression that aortic disease is associated with a greater risk than mitral disease. It would be wise to deal with a significant acquired or congenital valve lesion prior to elective surgery. Congestive heart failure, disorders of rhythm, and embolization are the most commonly encountered problems. A sudden drop in blood pressure or change in blood volume in a patient with significant aortic stenosis and fixed cardiac output may lead to intractable ventricular arrhythmia. Atrial fibrillation with rapid ventricular response may precipitate acute pulmonary edema in mitral stenosis. Antibiotic prophylaxis is indicated in all patients with acquired or congenital valvular disease or other congenital heart disease such as ventricular defect. Some object to prophylaxis in such situations, on the grounds that there are no conclusive studies to prove that it prevents endocarditis and that the risk of endocarditis is low. I believe that the potential benefit is so great and the hazard of treatment so minimal that there is no question that antibiotic prophylaxis should be employed. The recommendations of the American Heart Association should be followed (20).

Mitral Valve Prolapse. Risk factors for noncardiac surgery in older patients with mitral valve prolapse have not been established. There is not even agreement on its incidence. The usefulness of antibiotic prophylaxis is questioned. For those patients with a confirmed diagnosis (preferably with echocardiographic support), I recommend such prophylaxis. The risk of prophylaxis is minimal and the cost small. The possible benefit is great (20).

Congenital Heart Disease. Congenital heart disease, other than valve disease, is less commonly encountered in the older patient. The character of the lesion is the factor of chief importance. Antibiotic prophylaxis should be employed (20). The usual measures for the control of failure, arrhythmias, and polycythemia are indicated. Dr. Morris Kleinfeld and I had extensive personal experience with elderly patients with congenital heart disease in the section of the Wyckoff Cardiac Clinic of Bellevue Hospital Center which was directed by the late Dr. Joseph Brumlik. In this period before corrective cardiac surgery was possible, and in patients who refused such corrective surgery and in those presenting after the optimal period for such correction, we found it was usually possible to carry patients through emergency surgery with close cooperation with the anesthesiologist and surgeon, intensive monitoring, and follow-up care (21).

Prosthetic Heart Valves. The important consideration is the functional status of the prosthetic valve, nontissue or tissue. Antibiotic prophylaxis is indicated without question. I would follow the American Heart Association's suggested outline (20). Petersdorf's alternative recommendations deserve mention (22). Most workers in cardiology and infectious disease support the American Heart Association's recommendations.

Anticoagulation is required on a long-term basis for nontissue prosthetic valves. The risk of bleeding if anticoagulation is continued must be balanced against the risk of thromboembolism if anticoagulation is stopped. Accepted practice is stopping Coumadin 1–3 days before operation and resuming it 1–5 days postoperatively. The risk of thromboembolism is somewhat greater with mitral prostheses. Heparin is used for patients unable to take oral medications postoperatively. Prothrombin times and partial thromboplastin time determinations and careful observation for oozing or bleeding are important. Aspirin should be withheld prior to elective surgery for at least 7 days.

Cardiomyopathy. Little has been published on experience in noncardiac surgery for patients with cardiomyopathy, including that variant termed idiopathic hypertrophic subaortic stenosis. Antibiotic prophylaxis is in order because of the likelihood of aortic or mitral valve abnormality with associated risk for infective endocarditis. Sympathetic stimulation by an anesthetic agent is a risk. Tachycardia following this augments the contractile state with reduction in left ventricular volume and accentuation of left ventricular obstruction and possible pulling of the mitral valve into the aortic outflow tract by the Venturi effect. This would lead to a relative reduction in blood volume. Much more information is needed. A recent three-issue series on cardiomyopathy in *Progress in Cardiovascular Disease* contains no reference to experience with noncardiac surgery (23).

Disorders of Rhythm. Cardiac arrhythmias are common in the perioperative period. They are associated with induction, intubation, suction, ocular stimulation, visceral traction, hypoxemia, and hypercarbia. They are generally not of great significance and respond to anesthetic management.

The likelihood of a significant disorder of rhythm is greater if the patient has structural heart disease. Rhythm other than sinus or atrial premature systoles or more than five ventricular premature systoles per minute at any time before operation were determined to be significant risk factors by Goldman and associates (4). This was the first such reported correlation with perioperative cardiac complications. Lown et al (24), Kotler et al (25), and Hinkle et al (26), among others, have linked frequent premature ventricular systoles with the likelihood of developing myocardial infarction or cardiac death. The patients with significant arrhythmia followed by Goldman died of causes other than observed ventricular arrhythmias. This may indicate that the ventricular rhythm abnormalities are important as a marker for more severe heart disease. Goldman also suggested that atrial premature systoles may indicate marginal cardiac reserve. The evidence for this was not presented.

Treatment of the rhythm disorders, other than anesthetic management, is dependent on the underlying disease.

Pacemakers. The indications for permanent pacing are not affected by noncardiac surgery. Wolf and Braunwald advise temporary pacemaker placement for bifascicular block, with type II second-degree AV block, for a history of unexplained syncope, or for transient complete AV block. A temporary pacemaker should always be available for emergency placement (6).

A permanent pacemaker in place may present problems in the conduct of surgery. Demand pacemakers may be affected by electromagnetic interference from the use of electrocautery, resulting in failure to pace. This risk can be lessened by placing the indifferent plate of the cautery unit as far as possible from the lead and pulse generator and by using the electrocautery in brief bursts. Many pacemakers may be converted from demand to fixed-rate mode by magnet. An electrocautery may also interfere with electrocardiographic monitoring.

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General Articles, Specialty Notes, and Students' Corner

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Glyburide-Induced Hypoglycemia in An Elderly Patient: Similarity of First-Generation and Second-Generation Sulfonylurea Agents

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Abstract

A 72-year-old patient with renal insufficiency and hepatic disease became hypoglycemic after receiving 2.5 mg of glyburide. Hypoglycemia was severe and prolonged in spite of the administration of 10% glucose with boluses of 50% dextrose. This patient's course plus other reported cases of glyburide-induced hypoglycemia demonstrate that the contraindications to the administration of sulfonylurea agents are similar for both first- and second-generation compounds.

Glyburide is a potent second-generation sulfonylurea agent that has been used in the treatment of mature-onset, nonketotic (type 2) diabetes mellitus in Europe for more than 10 years. Although its adverse effects have been reported to be of low prevalence, concern has been expressed that the frequency of hypoglycemia may be greater than that found with other sulfonylureas (1). Since this agent has just become available in the United States for the treatment of diabetes mellitus, we believe that the case of the patient with glyburide-induced hypoglycemia described below will be of interest to physicians, since the course of the patient clearly demonstrates that the contraindications to the use of second-generation sulfonylurea agents are similar to the contraindications for first-generation agents.

Report of a Case

A 72-year-old woman was admitted for evaluation of hypoglycemic coma. Five years previously, a diagnosis of diabetes mellitus was made and she was treated with an oral hypoglycemic agent. This medication was discontinued by the patient after several months. She received no other treatment for diabetes until 1 day prior to admission, when she was given glyburide by a physician in Tijuana, Mexico for glucosuria. She ingested 2.5 mg of the drug and within several hours developed diaphoresis and anxiety. On the day of admission she took an additional 2.5 mg of glyburide, which was again followed by weakness, diaphoresis, and marked somnolence. Because of the somnolence, paramedics were summoned and the patient received an intravenous bolus of 50% dextrose. Following this she awoke but remained lethargic.

The patient's medical history included malaria, a cholecystectomy, anemia treated by transfusions, and a hospitalization 18 months prior to her admission for syncope, gastrointestinal bleeding, and renal insufficiency. Besides glyburide, the patient was ingesting vitamins, iron, and an appetite stimulant, as well as a cholesterol-lowering agent which she received from a Mexican physician.

Physical examination at the time of admission revealed a blood pressure of 205/100 mm Hg, respiratory rate of 26 per minute, and temperature

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of 97.8°. Mild clubbing of her nails, bibasalar rales, and S4 gallop, and a grade IV/VI systolic ejection murmur as well as a II/VI blowing diastolic murmur were heard over the cardiac apex. She was also noted to have a cholecystectomy scar, mildly enlarged liver, and bilateral knee effusions. Neurologic examination revealed lethargy and bilateral decreased vibratory sensation in both lower extremities. There were no focal neurologic abnormalities.

Initial laboratory evaluation (following the bolus of 50% dextrose) included a plasma glucose of 116 mg/dl, serum bicarbonate of 14 mEq/L, BUN of 55 mg/dl, creatinine of 4.6 mg/dl, hematocrit of 28%, and hemoglobin of 9.1 gm/dl. Arterial blood gases on room air revealed a pO_2 of 69 mm Hg, pH of 7.30, and pCO_2 of 30 mm Hg. A moderate amount of glucose, 1+ protein, and no ketones were present in the urine. Serum sodium and potassium concentrations were normal.

An infusion of 5% dextrose was begun. Three hours after the initial examination, the patient again became unarousable. There were no focal neurologic deficits. Dextrostix estimation of blood sugar was 20–40 mg/dl. She received an intravenous bolus of 50% dextrose and immediately awakened. She again became unresponsive 2 hours later and became alert after receiving another bolus of 50% dextrose. Serum glucose prior to the second bolus of dextrose was 37 mg/dl. The intravenous infusion was changed to 10% dextrose. However, she continued to have recurrent episodes of loss of consciousness relieved by intravenous boluses of dextrose. She received a total of 12 such boluses over the initial 36 hours of hospitalization. Serum glucose concentrations at the time of loss of consciousness ranged between 37 and 62 mg/dl.

During the next 6 days she received a constant infusion of 10% dextrose and regular oral feedings with a low-protein diet. Her serum glucose range was 95–112 mg/dl fasting and 110–185 mg/dl randomly. She did not have any other episodes of loss of consciousness. On the 12th hospital day a 5-hour glucose tolerance test was normal. Concurrent insulin levels were normal in the fasting state; following oral glucose, the levels rose fourfold, peaking at one hour. A 48-hour fast revealed normal levels of glucose (68 mg/dl) and insulin (11 microunits/ml). Additional testing included serum amylase, magnesium, prothrombin time, thyroxine, calcium, phosphorus, total protein, albumin, LDH, SGOT, and bilirubin; all these findings were normal. Serum alkaline phosphatase and 5′ nucleotidase were markedly elevated, suggesting biliary tract or parenchymal liver disease. An intravenous cholangiogram revealed possible partial obstruction of the common bile duct. A liver scan was normal. The patient refused further evaluation of her liver function. Creatinine clearance was 4.9 cc/minute.

The patient was discharged fully ambulatory on Scholl's solution, folate, and Amphogel. She was seen 6 weeks after discharge without a significant change in her clinical status. A fasting serum glucose was 102 mg/dl at that time. She was then lost to follow-up.

Discussion

On a weight basis, glyburide is the most potent sulfonylurea agent available for treatment of type 2 diabetes mellitus. Five mg are approximately equivalent to 1 gm of tolbutamide, 500 mg of acetohexamide, or 250 mg of chlorpropamide. The recommended dose range of glyburide is 1.25–20 mg/day, given once or twice a day (2).

Between 45% and 92% of the administered dose of glyburide is absorbed from the gastrointestinal tract, and peak serum levels are reached two to four hours following an oral dose (3). The serum half-life varies from 2 to 6 hours and the lowest serum glucose levels in fasting subjects occur 3 hours following an oral dose (3, 4). In fed subjects, the highest plasma insulin levels and lowest serum glucose concentration occur in midafternoon (5). The duration of the effect is approximately 24 hours, as manifested by depressions of the serum glucose levels following a single oral dose. The drug is almost completely inactivated in the liver (3) and approximately 50% of the metabolites are excreted in the feces via biliary excretion and 50% is excreted in the urine. Renal insufficiency prolongs the half-life of glyburide and its metabolites (6, 7). To the best of our knowledge, excretion of the drug and its metabolites has not been studied in subjects with hepatic disease.

The patient reported above was treated with glyburide for presumed diabetes mellitus on the basis of glucosuria. She developed anxiety, diaphoresis, and obtundation within hours of taking 2.5 mg of glyburide on two separate occasions. After the second dose she had documented hypoglycemia lasting more than 36 hours and required large quantities of intravenous dextrose to maintain euglycemia. It was subsequently shown that she had normal glucose tolerance, normal fasting and postprandial serum insulin levels, renal insufficiency, and biliary tract or parenchymal liver disease. Thus, her hypoglycemia was felt to be secondary to glyburide administration in a patient with renal and hepatic disease.

Glyburide has been previously reported to cause severe hypoglycemia, and hypoglycemic deaths have been recorded (1). In a series of 5,053 diabetic patients who received glyburide, the prevalence of hypoglycemic reactions requiring discontinuation of therapy was 1.6% (8). Preliminary results of glyburide administration to more than 3,000 patients in the United States revealed hypoglycemia, or symptoms suggestive of hypoglycemia, in 5%; these symptoms were severe enough to require discontinuation of therapy in 1.3% of the patients (3).

Several features are characteristic of glyburide-induced hypoglycemia.

First, it occurs more commonly in elderly patients, even with doses as low as 2.5 mg (3).

Second, renal insufficiency appears to be a predisposing factor in some individuals (5).

Third, hypoglycemia often occurs after several weeks of treatment, even without a change in the dosage (5).

Fourth, hypoglycemia may occur at any time during the day, but often develops in the afternoon, even though meals are eaten on a regular basis (5). If patients miss breakfast or reduce their morning food intake, midmorning hypoglycemia may occur (9).

Fifth, the patient's history prior to the use of glyburide often includes the occurrence of hypoglycemia after administration of other oral antidiabetic agents.

Sixth, the hypoglycemic action of glyburide is potentiated by concurrent treatment with phenylbutazone, oxyphenbutazone, and sulphaphenazole (sulfonamide) (10) similar to the situation with the first-generation sulfonylurea agents.

Seventh, the experience with this patient emphasizes that, as with first-generation compounds (11), second-generation sulfonylurea agent-induced hypoglycemia may take days to clear even with persistent glucose administration.

And finally, if the cholesterol-lowering agent received in Mexico was clofibrate, then this hypolipidemic compound may potentiate the action of a second-generation sulfonylurea agent, as has been shown for the first-generation agents (12).

Thus, glyburide should probably be used with caution in elderly individuals and should definitely not be administered in patients with marked renal insufficiency. The effect of mild liver disease on this patient's course is more problematic.

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Gastric Neurilemmoma: Case Report

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Abstract

Neurilemmoma, also known as schwannoma, of the stomach is a rare pathologic entity with higher incidence in females, arising at any age. Clinically it can be an occasional finding during the evaluation of patients with dyspeptic complaints but it is more frequently diagnosed by the presence of its complications, such as hemorrhage into the stomach or to the celomic cavity. The reported case is exceedingly rare not only because of its gastric localization but also because the diagnosis followed perforation into the celomic cavity in a white, 69-year-old woman. The histologic diagnosis revealed a subserous neurilemmoma without any signs of malignancy.

Neurilemmoma of the gastrointestinal tract, also known as schwannoma, is a tumor that arises from dependence of schwann cells of the nervous sheath. Three types have been described (1): digestive neurilemmoma in generalized neurofibromatosis or Von Recklinghausen disease, easily recognized by multiple cutaneous tumors over the periferic nerves and by the characteristic cutaneous pigmentation; multiple digestive neurilemmoma (stomach, appendix, cecum, rectum); isolated digestive neurilemmoma.

The incidence of neurogenic gastric tumors ranges from 1% to 9%, with a mean of 4.3% among all benign tumors of the stomach (2). Among all gastric tumors identified before death, only 7% are benign. Of these, nearly 40% are benign neoplasia from the smooth muscle; the incidence of all other benign tumors is under 5%. Clearly, gastric neurilemmomas are uncommon (3).

Neurilemmoma of the stomach is a rare pathologic entity (2, 4–6), with higher incidence in females (5, 6), arising at any age (4). Its clinical presentation is varied. Sometimes it is an occasional finding during the evaluation of patients with dyspeptic complaints (4, 5) or, more frequently, it is diagnosed by its complications (1), such as hemorrhage into the stomach (5) or to the celomic cavity (6, 7). The neurilemmoma localization in the stomach is more frequently the gastric antrum or the gastric body (6), particularly in the lesser curvature (7).

Case Report. A 69-year-old white woman resorted to the hospital emergency service complaining of excruciating abdominal pains; the day before admission she had had epigastric pain and dizziness followed by vomiting. She reported postprandial fullness and epigastric tenderness, sometimes with vomiting, without melencor hematemesis. About eight years before she had been treated symptomatically with digestive enzymes and antacids, prescribed by her family physician.

At the hospital, the physical examination revealed an acute abdomen: axillary temperature, 37.2° C; a rigid, boardlike abdomen with gener-

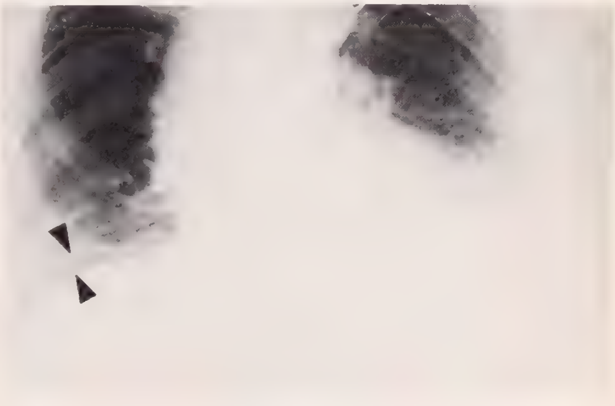

Fig. 1. Free air accumulated under each diaphragm, outlined between free air and lung base.

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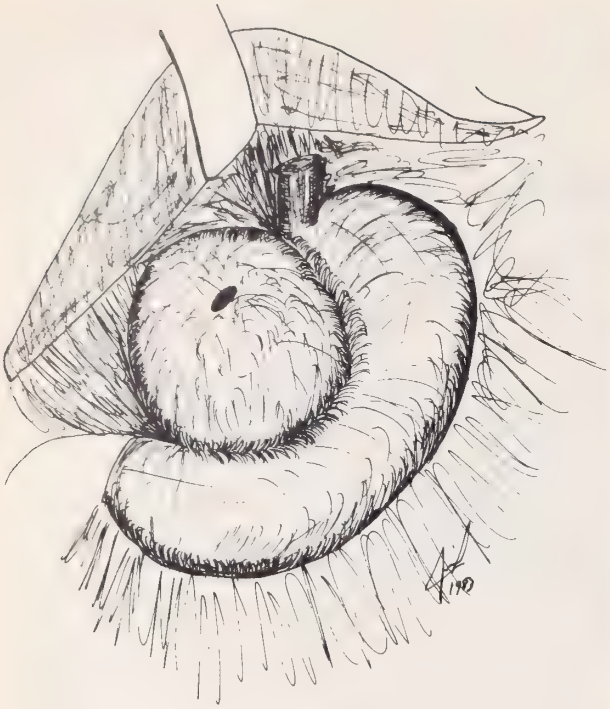


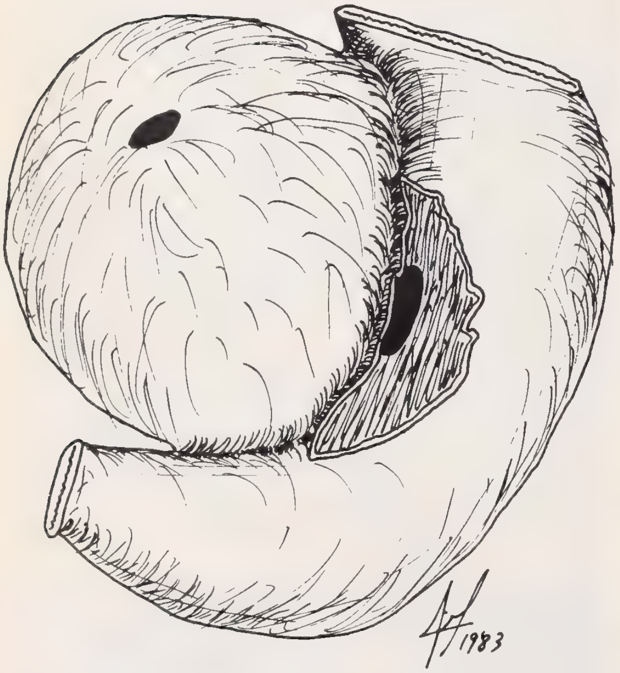
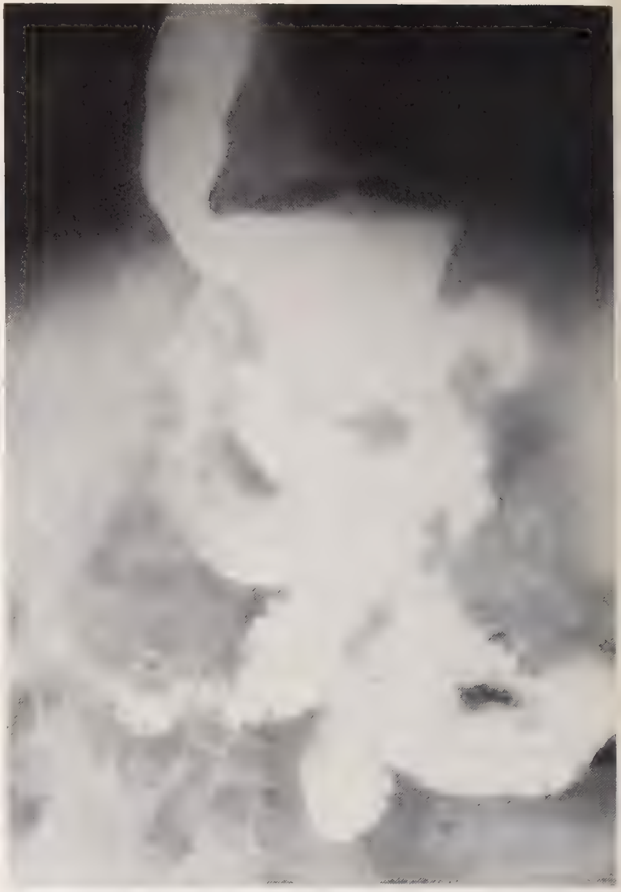


Fig. 2. Schematic representation of tumor into abdominal cavity.

Fig. 3. Tumor after subtotal resection.



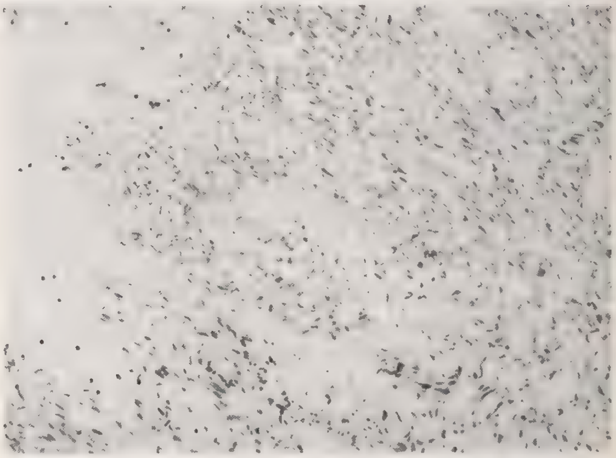


Fig. 4. Barium-contrast X-ray study of gastrojejunal anastomosis.

Fig. 5. Photomicrograph of tumor demonstrating Verocay bodies (hematoxylin and eosin ×20, slightly reduced).

alized rebound tenderness; bad general condition with dry skin and dry oral mucosa; discreet nasal fluttering; rapid filiform pulse; blood pressure, 100/50 mmHg; ECG, normal; Hb, 12 gm/dl; packed cell volume, 42%; leukocytes, 7,400/cu mm.

Pulmonary x-ray was normal; the simple abdominal x-ray in standing position showed subdiaphragmatic air-Jobert sign (Fig. 1). Nasogastric suction yielded no blood.

Perforation of duodenal ulcer into the peritoneal cavity was considered the most likely diagnosis, so laparotomy was performed.

Surgical Operation. A supraumbilical medial longitudinal incision was made. In the celomic cavity there was a round tumor with a bulging surface, about 15 cm in diameter, subserosal on the small curvature of the stomach with ulceration facing the left lobe of the liver (Figs. 2, 3). There were discreet signs of diffuse peritonitis in the upper stage of the abdomen. The peritoneal cavity contained about 300 cc of serous bloody fluid.

After four-fifth gastrectomy, gastric continuity was reconstructed with Billroth II, anterior Polya anastomosis, with omega Braun's loop.

The patient was discharged after 20 days, without complications. Subsequent radiographic study (Fig. 4) showed well-functioning anastomosis and the patient has had no complaints for the last year.

The histologic diagnosis performed by Prof. Daniel Serrão revealed a subserosal neurilemmoma without signs of malignancy (Fig. 5).

Discussion. Clinical diagnosis of gastric neurilemmoma is quite difficult because of its uncharacteristic signs and symptoms and generally comes about only by its complications, such as hemorrhage or perforation. Even during surgical exploration the exact diagnosis of neurilemmoma is not an easy one because the gross appearance of the tumor is quite similar to other gastric neurogenic tumors (neurofibroma and neurofibrosarcoma) or leiomioma.

Histologic diagnosis may require special coloration technique to distinguish neurilemmoma from leiomioma.

Prognosis is generally good.

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Cardiotoxic Effects of Chemicals

Steven F. Horowitz, M.D., FACC, Deborah Matza, RN, and Josef Machac, M.D.

Toxic influences on the heart can result in diffuse or multicentric myocardial injury. Signs and symptoms of congestive heart failure may develop, and, in more severe cases, fulminant, rapidly progressive cardiomyopathy can result in death within days or weeks of initial onset of symptoms (1).

The term "cardiomyopathy" has previously been reserved for idiopathic dysfunction of the myocardium (2, 3). In this review, we use the term as more broadly defined by Johnson and Palacios (4), that is, heart failure resulting directly from a primary myocardial disease, not from the effects of a concomitant condition such as valvular insufficiency or hypertension.

Pathophysiology. Several types of cardiomyopathies are chemically induced; the most common is dilated cardiomyopathy. This is characterized by abnormal systolic function, a reduced left (and often right) ventricular ejection fraction, and enlargement of the ventricular chambers. The left ventricular ejection fraction may be reduced by 10% or more before symptoms of congestive heart failure become evident. Dysfunction of the right ventricle is not invariable. When it occurs, it can either be the direct result of myopathic involvement of the right ventricular myocardium or of increased right ventricular afterload caused by the transmission of high left-sided pressures through the pulmonary artery. Similarly, cardiac chamber enlargement may result either from primary myocardial involvement and associated compensatory dilatation, or from progressive chronic pressure and volume overload originating from a failing left ventricle. Enlargement of all four cardiac chambers is a common finding in the end-stage of dilated cardiomyopathy. Although the ejection fraction can be markedly depressed and the end-diastolic pressure elevated as the left ventricle dilates, resting stroke volume and cardiac output may be relatively well preserved until the later stages of the disease.

Mitral insufficiency is frequently present in the dilated left ventricle (5), due to annulus dilatation and poor valve coaptation. Papillary muscles are realigned as a consequence of increasing ventricular globularity. The mitral insufficiency caused by dilated cardiomyopathy is usually not severe, and since most patients with primary mitral insufficiency retain good myocardial function, the differential diagnosis is readily apparent. However, some patients with primary mitral insufficiency develop severe myocardial dysfunction during the advanced stages of their disease. In these patients, it is quite difficult to elucidate the etiology of their myocardial dysfunction.

Deterioration of myocytes and progressive interstitial fibrosis generally result in diffuse hypokinesis of the ventricle. However, regional asynergy can occur (6), and focal areas of more severe involvement are commonly found at autopsy or myocardial biopsy. Intracardiac thrombus formation is commonly encountered at necropsy (7). Although in coronary artery disease mural thrombi rarely embolize, in the dilated cardiomyopathies clinically significant embolization is fairly common.

Types of cardiomyopathies (other than the dilated type) induced by chemical agents are considerably less common. Restrictive cardiomyopathy, for example, occurs as a result of iron overload (8). In this situation, elevation of pulmonary venous pressure may occur without significant ventricular dilatation or systolic dys-

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function. The main abnormality is related to left ventricular compliance, manifested by impaired diastolic filling.

Clinical Findings. The usual symptoms are breathlessness, fatigue, palpitations, and, occasionally, chest pain. Physical examination reveals signs of failure of the left side of the heart with or without failure of the right side (9). An S_3 or summation gallop is usually present when congestive failure is clinically evident (10). The chest X-ray shows cardiac enlargement and pulmonary congestion. The electrocardiogram is invariably abnormal, showing nonspecific S-T segment and T-wave abnormalities, left ventricular hypertrophy, left bundle branch block, poor R wave progression, or pseudoinfarction patterns with pathologic Q waves (11, 12). Atrial fibrillation may occur in one of six patients, and ventricular arrhythmias ranging from isolated ventricular premature beats to unsustained and sustained ventricular tachycardia are frequently present (13).

Cobalt. In 1965, Kesteloot et al described a perimyocardiopathy in heavy beer drinkers in Belgium (14). Although alcoholic cardiomyopathies had been known for some time, the authors suggested that this was a distinct syndrome because of the presence of a disproportionately large pericardial effusion (15). Shortly afterward, investigators in Quebec reported a number of similar cases occurring as a fulminant disease in heavy beer drinkers (16–18).

Additional clinical features that appear to be characteristic of "beer-drinkers' cardiomyopathy" include poor R wave voltage on ECG (even in the absence of large pericardial effusion) and an unusually low incidence of arrhythmias (19). Higher than normal hemoglobin concentrations were also present, probably related to the stimulatory effect of cobalt on erythropoiesis. Cobalt chloride has been used therapeutically in anemic patients (20).

The Canadian investigators raised the possibility that cobalt, a beer additive used to control foaming, was in fact responsible for this new cardiac entity. Pathologic studies on 20 patients (21) revealed hypertrophy of all cardiac walls, slight chamber dilatation, and mural thrombi in 40% of specimens. There was no evidence of active myocarditis on microscopic examination. There was a decrease in myofibrils, increased vacuolization and interstitial edema, and a somewhat unusual increase in myocardial glycogen.

Cobalt is capable of interfering with the breakdown of metabolites in the Krebs cycle and the metabolism of pyruvate. It inhibits several enzymes, possibly by competing with calcium and magnesium ions (22, 23). Despite the epidemiologic relationship of cobalt salt intake and cardiomyopathy, it appears likely that cofactors are required to produce clinically manifest illness. All patients encountered with the disease have been long-standing, heavy beer drinkers; the average for such patients is often an astonishing 20 or more pints of beer per day. However, animal experiments suggest that protein deficiency can potentiate the myocardial effects of cobalt (24).

In the absence of cofactors, cobalt cardiomyopathy appears to be rare. Only isolated cases of cobalt cardiomyopathy have been reported after industrial exposure (25). Additional evidence is provided by our own study (26) involving rest and exercise radionuclide evaluation of left ventricular function in a group of hard-metal workers occupationally exposed to airborne cobalt dust. Despite prolonged exposure and evidence of interstitial pulmonary fibrosis in some subjects, left ventricular function was essentially normal, both at rest and with supine bicycle exercise.

Ethanol. Chronic alcohol ingestion was first implicated as a cause of cardiac disease nearly 130 years ago (27). Although a relationship between cardiomyopathy and prolonged ingestion of wine, beer, and whiskey has been known for years, the precise mechanism of alcohol-induced cardiac disease remains controversial. There is evidence that rapid administration of ethanol to experimental animals produces acute depression of myocardial contractility (28). This is accompanied by the typical hemodynamic findings of clinically encountered cardiomyopathies: elevated left ventricular end-diastolic pressure, diminished stroke volume, and an abnormal rate of contraction (dp/dt). There is biochemical and electron microscopic evidence for a decrease in several mitochondrial oxidative enzymes in patients with alcoholic cardiomyopathy (29, 30).

The clinical findings are similar to those in other congestive cardiomyopathies. In addition to ventricular arrhythmias, supraventricular arrhythmias are common. Atrial fibrillation may occur as a consequence of acute alcoholic ingestion in otherwise healthy people (the so-called holiday heart syndrome).

Despite the apparent relationship between prolonged ethanol ingestion and cardiomyopathy, the disease remains rare among chronic alcoholics. Many authors believe cofactors are necessary to produce clinical manifestations of congestive failure (31). Alcoholics are more susceptible to infection, and the cardiomyopathy may represent previous viral myocarditis (32). In addition, alcoholics have multiple metabolic and nutritional disorders that can potentiate the effects of alcohol.

Lead. Increased cardiovascular mortality has been reported among persons with occupational exposure to lead (33, 34). It is not clear whether this is caused by the higher incidence of hypertension thought to be associated with lead intoxication (35), or by increased coronary atherosclerosis related to lead (36, 37). The evidence remains inconclusive.

Anthracycline Antibiotics. Several new cancer chemotherapeutic agents have been associated with irreversible cardiomyopathy (38). The anthracycline group of antibiotics, including doxorubicin (Adriamycin) and daunorubicin, are cardiotoxic in a somewhat dose-related manner (Fig. 1).

Cardiotoxicity is unusual at cumulative doses of Adriamycin lower than 450–550 mg/m^2. Higher doses are usually tolerated well, and severe congestive heart failure can be prevented by close monitoring of ventricular function with serial ultrasound or radionuclide ventriculography (Fig. 2). The toxic cardiac manifestations can be acute and transient (including nonspecific ECG changes and arrhythmias), or may occur a month or more after the last drug dose was administered (39–41). In the latter situation, patients often have a severe and fulminant clinical course that responds poorly to standard therapy and carries high mortality. Pretreatment with radiation, which is independently cardiotoxic, can potentiate the deleterious effects of Adriamycin on the heart (42).

Anthracyclines act therapeutically through intercalation with DNA but their cardiotoxic effects may be related to other factors, such as calcium-mediated myocardial necrosis or the production of superoxides (43). Evidence of myocyte damage by microscopic examination is found relatively early in the course of Adriamycin therapy (44), usually before other laboratory and clinical evidence for myocardial dysfunction becomes ap-

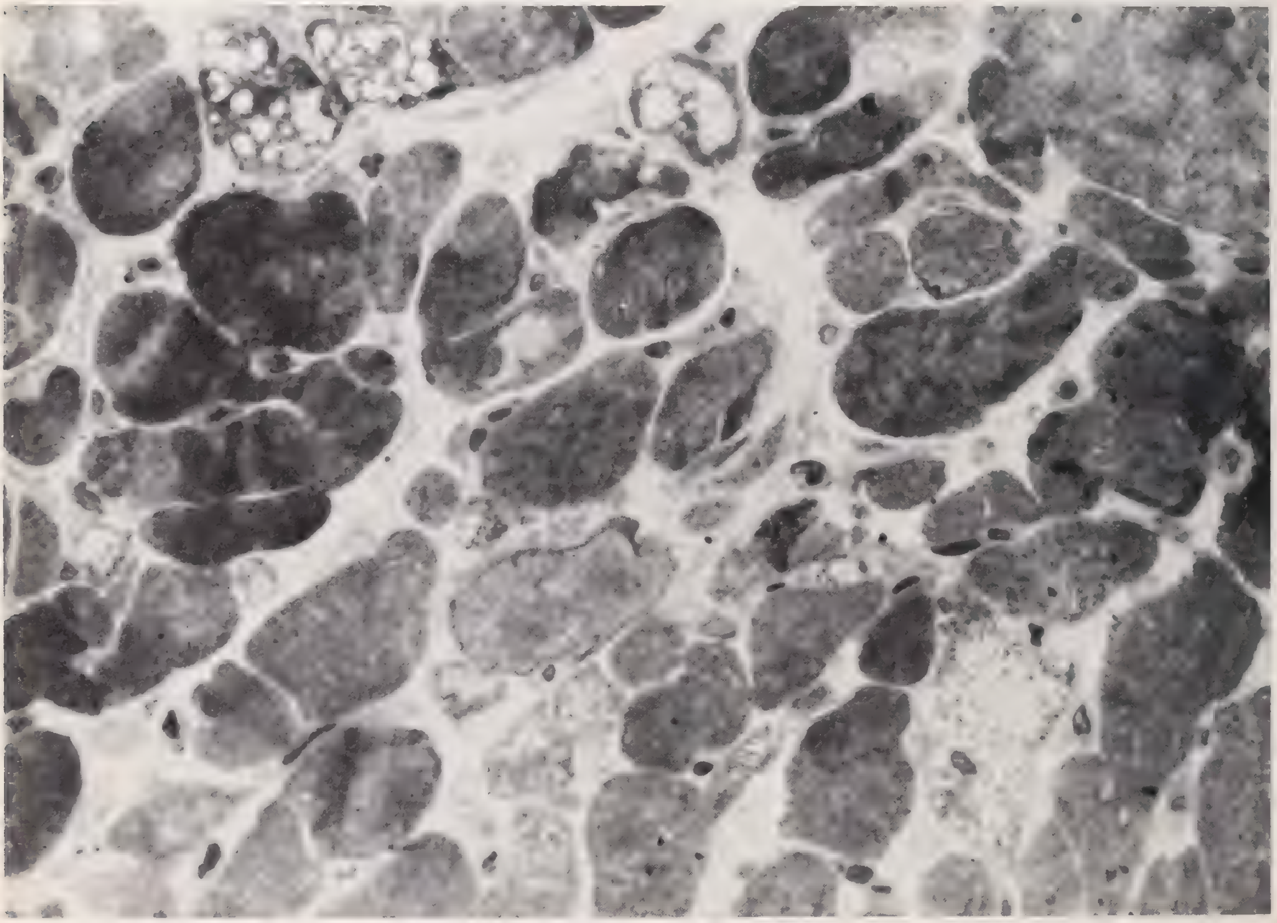

Fig. 1. Low-power (× 40, original magnification) photomicrograph of rabbit myocardium showing typical cellular changes of Adriamycin toxicity, including myofibrillar lysis and dilatation of sarcoplasmic reticulum.

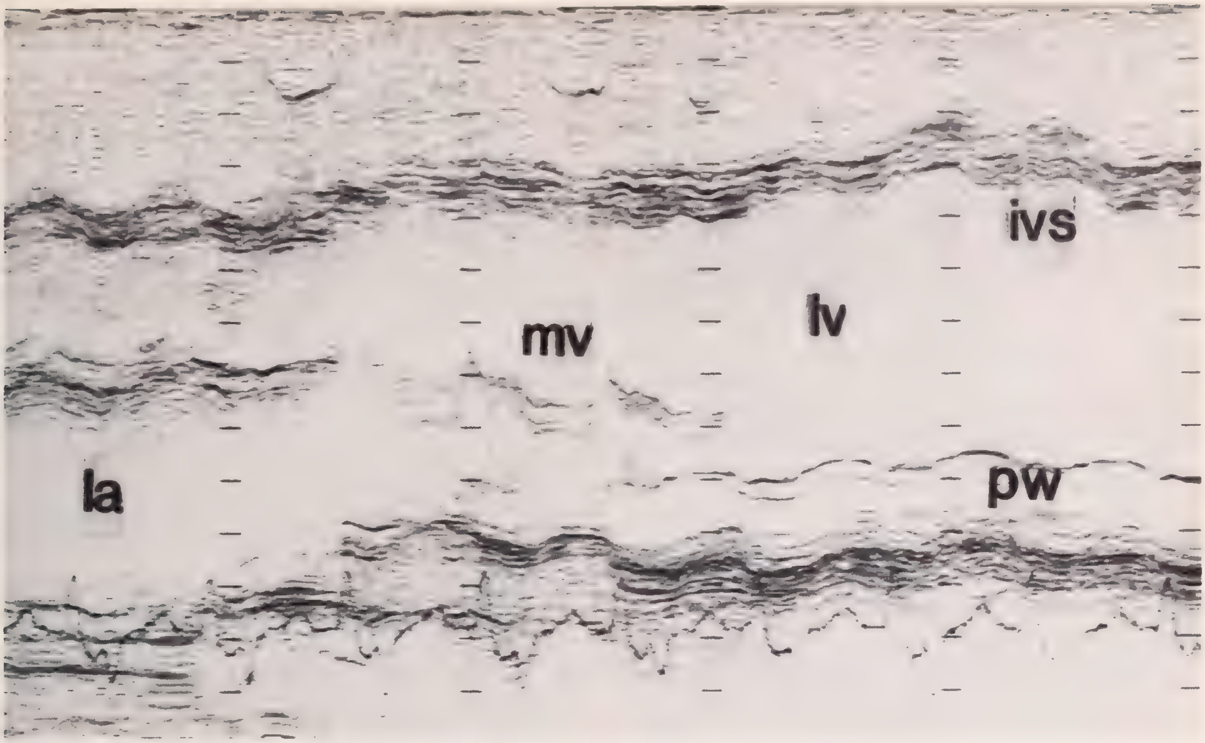

Fig. 2. M-mode echocardiogram of dilated cardiomyopathy showing hypokinesis of septum (ivs) and posterior left ventricular wall (pw). Mitral valve (mv) appears to be floating in enlarged left ventricular cavity (lv). Left atrium (la) is enlarged from secondary mitral insufficiency.

parent. Serial noninvasive tests can require cessation of therapy before the occurrence of cardiomyopathy, and can result in premature cessation of needed medication.

Selected patients who require additional chemotherapy but who have early, asymptomatic noninvasive test abnormalities, may benefit from additional Adriamycin while under close observation for clinical signs of congestive failure. The prophylactic use of cardiac glycosides and vitamin E to prevent cardiotoxic effects remains controversial.

Other Cardiotoxic Agents. A great number of chemicals have been suspected of causing cardiac disease, including several trace metals. An abnormally high zinc-to-copper ratio, for instance, has been found in hypertensive subjects, and Klevay (45) reported a higher than normal ratio in the myocardial tissue of patients with coronary artery disease. He proposed that the beneficial effects of increased physical activity might be from zinc loss through sweating. Similarly, intake of hard water, which has been associated with a lower incidence of coronary disease, causes a decrease in zinc-to-copper ratio. While interesting, these findings remain controversial and unproven (46), as do also the findings on other trace elements, such as cadmium, thought to be associated with hypertension.

Cigarette smoking, long associated with increased risk of coronary artery disease, has recently also been associated with increased risk of cardiomyopathy. Hartz and co-workers (47) demonstrated that men under the age of 55 have an increased incidence of both diffuse and regional asynergy unrelated to the association of smoking with coronary stenoses. The proposed mechanisms include nicotine and carbon monoxide injury of myocytes, damage to small vessels, and enhanced susceptibility to viral infection.

Other drugs, such as sulfonamides, heroin, steroids, catecholamines, and amphetamines, have cardiotoxic potential (48). There is also some evidence that occupational exposure to carbon disulfide can cause coronary artery disease (49, 50).

Halogenated hydrocarbons used in aerosol propellants have been implicated in the genesis of cardiac arrhythmias (51, 52). Trichloroethylene and fleuroalkane are known as freons. More than 100 adolescents have died shortly after inhaling freon gases from aerosol cans (53). A study by Speizer et al (54) demonstrated a relationship between occupational freon inhalation in hospital workers and increased frequency of palpitations.

The withdrawal of some chemicals precipitates cardiac disease. This is the case with workers exposed to nitroglycerin, ethylene glycol dinitrate, and other aliphatic nitrates with vasoactive effects. Workers have suffered an increased incidence of coronary spasm, myocardial infarction, and arrhythmias within 72 hours of withdrawal from nitrates. A Swedish study suggests a prolonged risk, months or years after exposure has been terminated, suggesting other mechanisms in addition to coronary spasm.

Keshan disease is a dilated cardiomyopathy of young people in a well-circumscribed region of China (55). There appear to be significant data pointing toward deficiency of selenium in the diet as a principal cause.

Indirect Cardiac Effects. A number of chemicals may indirectly affect the heart by causing hemolysis or methemoglobinemia. This latter group includes dinitrobenzene, toluidine, aniline, and trinitrotoluene (56). Any agent causing pneumoconiosis can be considered to affect the heart by producing cor pulmonale with right ventricular enlargement and dysfunction. Such agents include asbestos, silica, aluminum, talc, mica, coal dust, hay and grain dust, and hard metals such as tungsten and cobalt (57–59).

Summary. Numerous chemicals found in the environment have now been identified as cardiotoxic agents, and many more are suspected but as yet unproven. In view of the continued introduction of new chemicals into the environment and the increasing sensitivity of diagnostic methods to detect myocardial dysfunction, it seems likely that additional cardiotoxic agents will be uncovered. The search may produce insight into the large percentage of dilated cardiomyopathies that occur each year without a clearly identifiable etiology.

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Case Report: Ultrasonographic Features of "Milk of Calcium" in Kidney

EVANGELOS DIAKOUMAKIS, M.D., ULRICK VIEUX, M.D., BURTON SEIFE, M.D., AND THOMAS C. SNYDER, M.D.

Case Report. A 50-year-old Oriental man was admitted to City Hospital Center at Elmhurst with a three-day history of dizziness and melena. The patient had taken aspirin shortly before the onset of symptoms. His medical history included a report of untreated hypertension.

Physical examination revealed blood pressure 90/70, pulse rate 96/min. The abdomen was soft, nontender, and free of organomegaly. The nasogastric aspirate was described as "coffee-grounds," and the stool guaiac was positive. HCT and HGB were low, and on endoscopy a duodenal ulcer was diagnosed. The patient was treated with cimetiden and antacids, and given a transfusion of packed red cells. His bleeding stopped.

The chest roentgenogram on admission was normal and an abdominal film (Fig. 1) showed a radiopaque density overlying the left renal outline. An abdominal sonogram was performed because of this finding. The transverse scan in right lateral decubitus position and the longitudinal scan in the supine position both demonstrated a parapelvic cyst with layering dense echoes in the most dependent portion accompanied by acoustic shadowing (Fig. 2). The diagnosis of milk of calcium was made and an excretory urogram (Fig. 3) confirmed the diagnosis.

Discussion. Milk of calcium in the kidney is indeed quite unusual. The present case is the third sonographic demonstration of this entity in the urinary tract reported in the English-language literature.

"Milk of calcium" is a suspension of fine particles of precipitated calcium salts that concentrate in the most dependent portion of a fluid-filled space. The finding is known to occur more frequently in the gallbladder. In the kidney, a calyceal diverticulum or pyelogenic cyst is the most common location for the formation of a milk-of-calcium suspension of salts (1). The finding has also been described in renal cysts and in hydronephrosis (2–6).

A calyceal diverticulum or pyelogenic cyst is

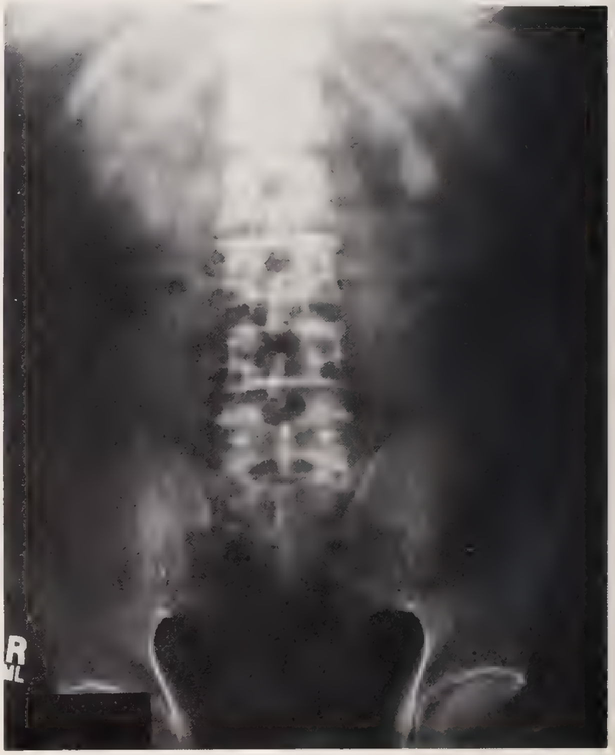

Fig. 1. Abdominal radiograph: an ovoid opacity overlying left renal shadow below left 12th rib.

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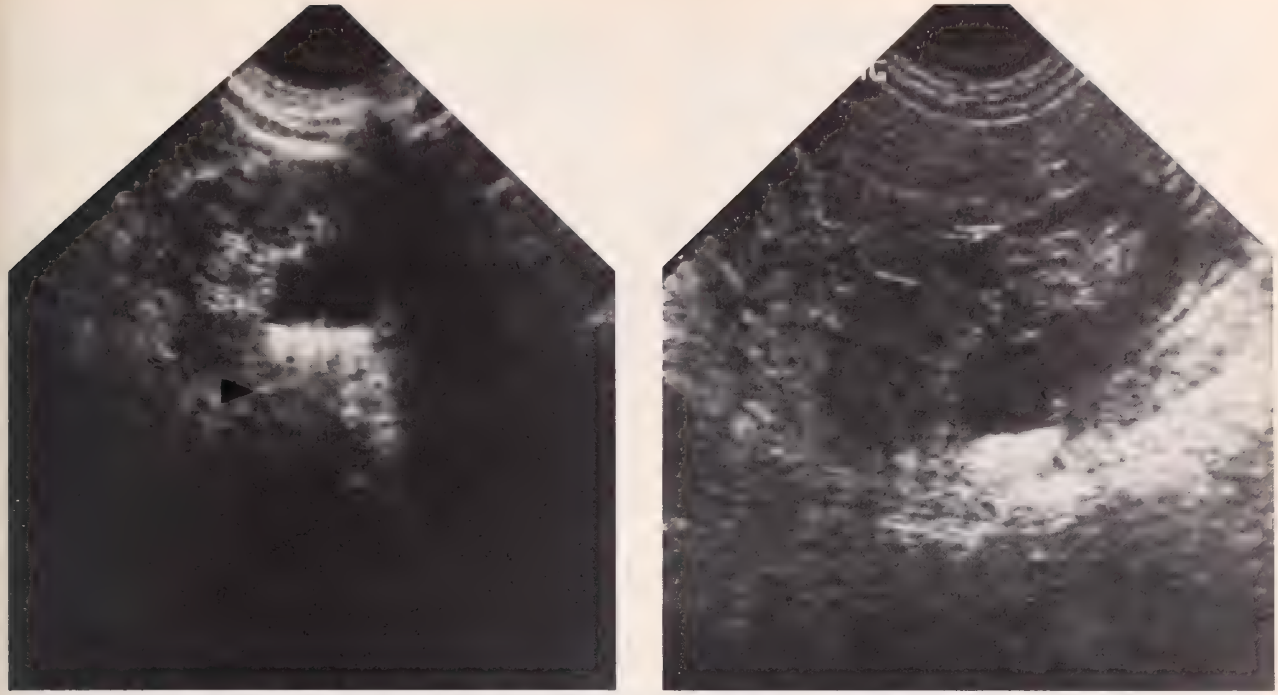

Fig. 2. Renal ultrasonography showing parapelvic cyst with layering dense echoes in most dependent portion accompanied by acoustic shadowings (arrow). **Left** Transverse scan in right lateral decubitus position. **Right** Longitudinal scan in supine position.

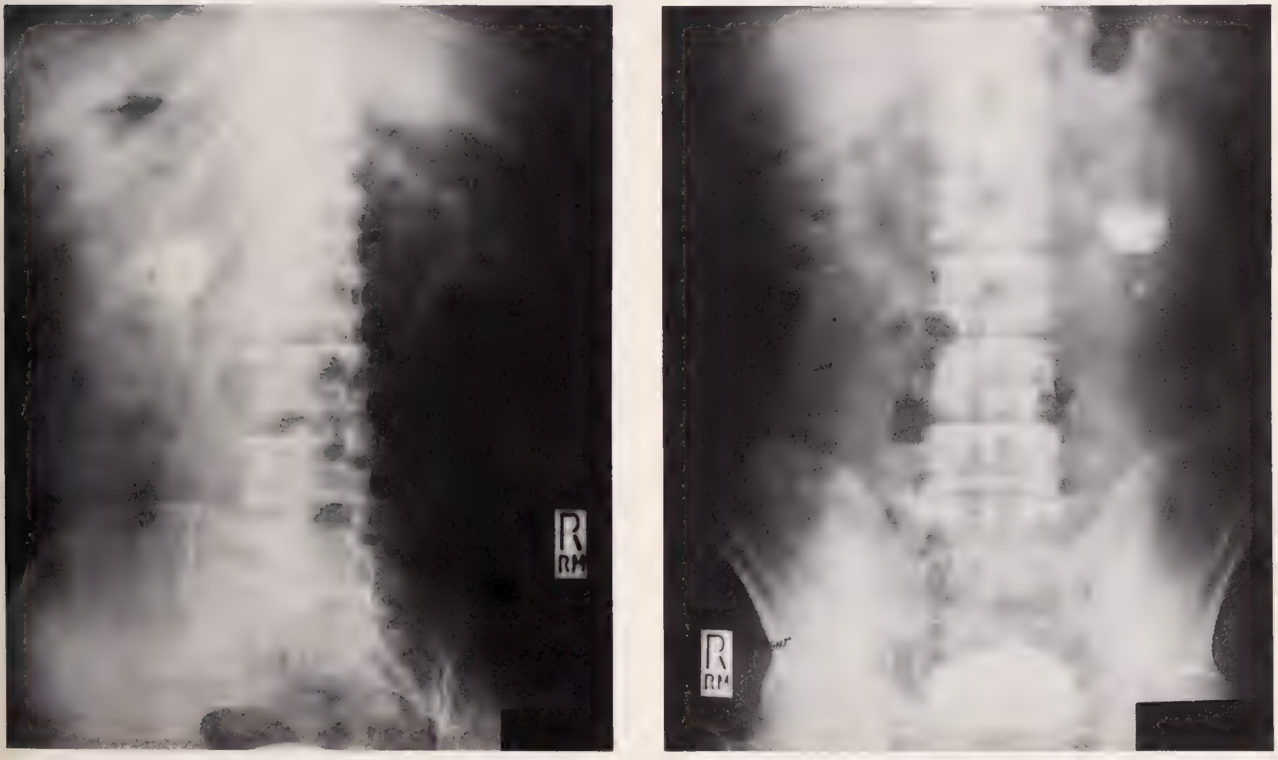

Fig. 3. Intravenous urogram. **Left** Left posterior oblique. **Right** Erect projection shows layering of parapelvic density. Apparent increase in size of density compared to original abdominal film is due to addition of contrast within cyst.

differentiated from a simple renal cyst by its content, location, and epithelial lining (7). The calyceal diverticulum is believed by some to originate from the Wolffian duct system and is lined with transitional cell epithelium. The urine that fills the cyst is the result of its communication with the pelvocalyceal system or the presence of collecting tubules located within its wall. It is therefore understandable that the volume of the collection within the cyst may increase during contrast urography as a result of either osmotic diuresis or back seepage of contrast from the calyceal system (8). This phenomenon was noted in our patient (Fig. 3).

In the past, the diagnosis of "milk of calcium" was based on the appearance of the preliminary film of the abdomen and on excretory urography (9). Reliance was placed on the size, configuration, and appreciation of the layered appearance of the opaque collection.

The sonographic pattern is also relatively specific, consisting of dense echoes in the dependent part of the lesions associated with acoustic shadowing (10). The echoes shift with position changes. The acoustic shadows are produced by the calcium content within the cyst (Fig. 2).

The prognosis for patients with milk of calcium is good. The condition is usually associated with an absence of symptoms. In one reported case, the lesion underwent spontaneous diminution in size during a three-year period. It was thought that the calcium particles drained from the cyst (11). Recognition of this lesion as a benign entity is important in order to avoid unnecessary and prolonged diagnostic studies.

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Case Report: Milk of Calcium in the Kidney after Cyst Puncture

Peter H. Tey, M.D., Afzal Ahmed, M.D., and K. F. Chan, M.D.

Case Report. A 69-year-old man was admitted because of a transient cerebral ischemic attack consisting of left-sided weakness. Several years previously a radiolucent benign cyst in the left kidney was diagnosed on intravenous urography (Fig. 1) and renal arteriography. A cyst puncture followed by instillation of Renografin 60 into the cyst was performed. Subsequent studies taken two years after the instillation of contrast into the cyst revealed a large dense opacification within the left kidney (Fig. 2).

Physical examination on the present admission was unremarkable. Blood chemistry studies revealed blood urea nitrogen 21 mg%, glucose 450 mg%, calcium 10.6 mg%, creatinine 15 mg%, lactic acid dehydrogenase 266 units.

An intravenous urogram again revealed a calcified mass in the upper pole of the left kidney (Fig. 3). A renal cyst containing milk of calcium was suspected. A horizontal beam radiograph taken with the patient in the upright position failed to reveal any change in the overall appearance of the lesion or layering of the cyst content. A sonogram, however, showed the lesion to be cystic. Cyst puncture revealed straw-colored opalescent fluid and double-contrast studies using Renografin 60 and air demonstrated a smooth-walled renal cyst. Analysis of the cyst fluid revealed total protein 1.5 mg%, LDH 6.0 units, and glucose 921 mg%. The sediment consisted of calcium carbonate and phosphate crystals.

Discussion. The existence of milk of calcium lesions has been known for some time. The lesion was first described in the gallbladder with cystic duct obstruction. Milk of calcium in the kidneys (1–3, 7), the ureters (5), and the pancreas (8) have also been reported. Various observers have stressed the "layering" effect of milk of calcium, caused by sedimentation of calcium salt crystals, as a diagnostic feature for these lesions (6); surprisingly, this feature was not present in our case.

The pathogenesis of milk of calcium is not fully understood. It is usually found in epithelial-lined cavities associated with impaired drainage, for

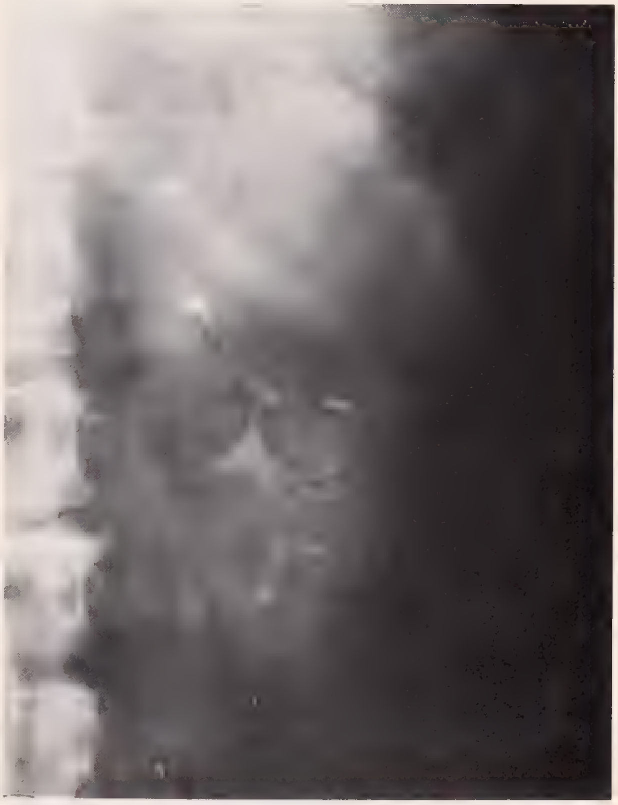
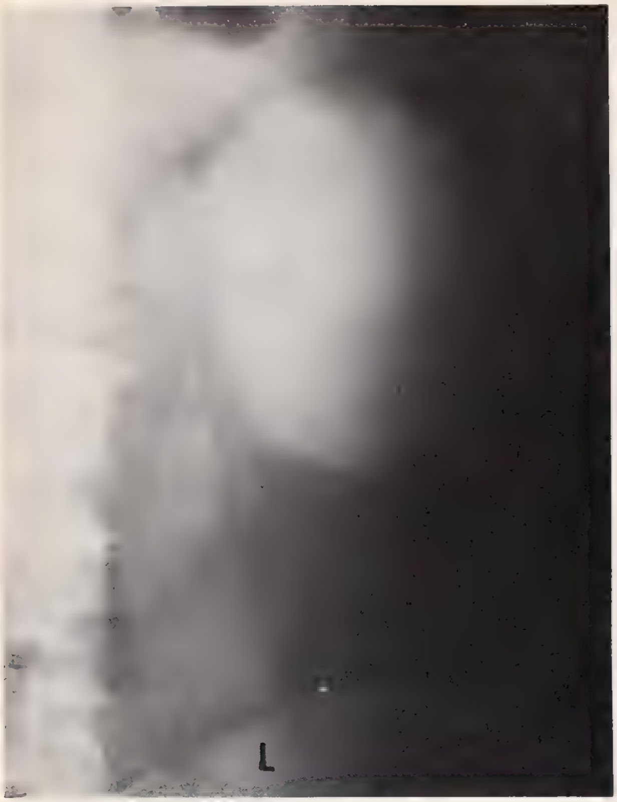


Fig. 1. Intravenous urogram demonstrates space-occupying mass in upper pole of left kidney.

From the Radiology Service, Bronx VA Medical Center, Bronx, NY 10468.



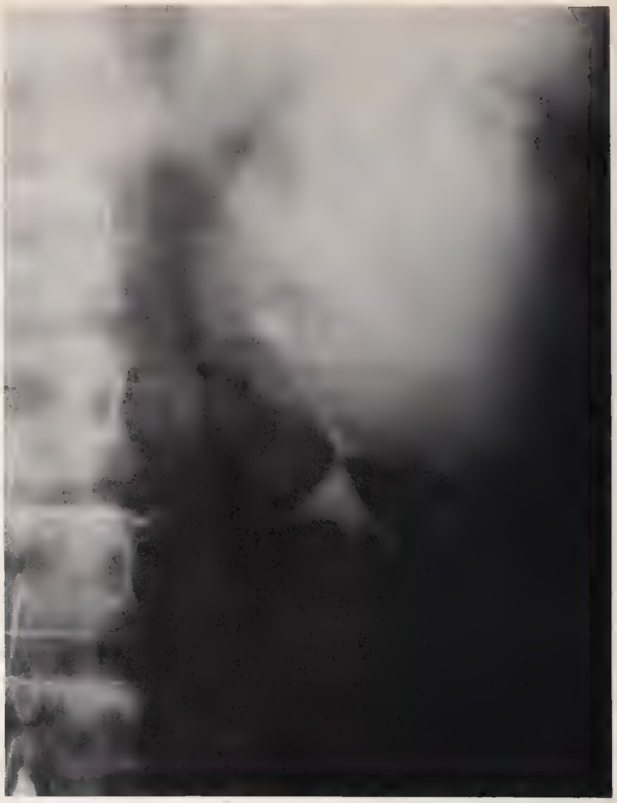


Fig. 2. Left Abdominal film taken 2 years later shows large calcified mass in left upper quadrant. No evidence of layering.

Fig. 3. Right Intravenous urogram again shows densely calcified cyst.

example the gallbladder with cystic duct obstruction, calyceal diverticula, pyelogenic cysts, hydronephrosis, hydroureter and pancreatic pseudocysts. The combination of inadequate drainage and superimposed chronic inflammatory changes in these lesions probably induces the precipitation of calcium salts. It is conceivable that because of the temporal proximity to the production of milk of calcium, the cyst puncture performed in our patient may have caused some degree of inflammation within the renal cyst.

Differential diagnosis of milk of calcium lesions on abdominal roentgenograms include calcified cysts and large calculi. The homogeneous opaque density on the abdominal film in our case suggested milk of calcium despite the absence of layering. This diagnosis was suggested not only by the radiographic findings but by the change in density of the cyst during the previous years. In addition, a ringlike peripheral calcified density is more typical of a calcified cyst. The obvious size and configuration of the dense mass did not suggest a renal calculus.

The characteristic layering effect of milk of calcium was not observed in our patient, although fluid recovered from the cyst puncture showed abundant calcium carbonate and phosphate crystals. Sedimentation of calcium salts depend on size, electrical change, and the relative specific gravity of the particles in relation to the solvent. The absence of layering is not surprising in this case, inasmuch as the specific gravity of cyst fluid was elevated because of the high glucose content. The latter is due more to the patient's diabetes than to the effect of increasing cyst expansion as observed by Lang (4). In our patient the size of the renal cyst remained unchanged for seven years.

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Surgery Notes

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Gastric Inflammatory Pseudotumor

KENT E. SKOGERSON, M.D., ALLEN J. FREDLAND, M.D., AND MOHAN C. AIRAN, M.D.

Gastic inflammatory pseudotumor, which is encountered in the wall of the stomach, is a rare nonneoplastic lesion that may mimic malignancy. In the case reported on here, a benign gastric polyp was responsible for gastrointestinal hemorrhage and pyloric obstruction.

Case Report. The patient was a 66-year-old black woman, evaluated for gastrointestinal bleeding. She had been having melanotic stools for two weeks and also complained of dyspnea on exertion, weakness, and dizziness with epigastric burning pain. She reported having hypertension for eight years and arthritis for several months. She had had a cholecystectomy in 1965 for cholelithiasis. She was a nonsmoker and a nondrinker. She was allergic to penicillin and streptomycin. On physical examination, she was well-developed and slightly obese. Her vital signs were normal. She was tender in the epigastrium but no abdominal masses were palpable. Findings on her laboratory studies included hemoglobin, 5.0 and hematocrit, 16.2. An upper gastrointestinal examination showed a small hiatal hernia with a large filling defect of the duodenum, indicating a possible large polyp. Gastroscopy revealed a large benign-appearing lesion prolapsing through the pylorus and into the duodenum. Brushings showed atypia secondary to inflammation.

Endoscopic findings were negative for any active bleeding. However, the patient went on to require five units of packed red blood cells while hospitalized. Lower gastrointestinal examination and colonoscopy revealed no abnormalities.

At laparotomy, a pedunculated 10-cm long, 2-cm wide polyp with inflammatory changes was excised with wide margins through a gastrotomy. The patient did well postoperatively and was discharged from the hospital one week later.

Discussion. This patient's tumor was identified as an inflammatory pseudotumor, which has also been described as inflammatory fibroid polyp, eosinophilic granuloma, eosinophilic gastritis, and gastric submucosal granuloma with eosinophilic infiltration.

Inflammatory pseudotumors of the stomach appear as either polypoid or infiltrative lesions, usually located in the antrum of the stomach. The tumor is usually soft and rubbery and several centimeters in length. The mucous membrane is usually ulcerative. When cut, the lesion may be pink, yellow, or white. Histologically, it is inflammatory with vascular proliferation and predominant eosinophilic infiltration.

Inflammatory pseudotumors may present with abdominal pain, anemia, melena, or obstruction. X-rays reveal a polypoid filling defect or an antral deformity.

Epithelial polyps constitute approximately 75% of the accompanying list; with mesenchymal neoplasms and miscellaneous tumors accounting for half each of the remainder.

One type of benign tumor is found to coexist with carcinoma of the stomach. Thus, the discovery of epithelial polyps should serve to warn the physician which patients are at increased risk of developing cancer. These patients should be examined at regular intervals by air-contrast studies or endoscopy or both.

In sum, the classification of polyps is as follows:

1. Epithelial Polyps
   Hyperplastic
   Adenomatous
2. Mesenchymal Neoplasms
   Leiomyomas
   Fibromas
   Osteomas and Osteochrondromas
3. Miscellaneous Tumors
   Aberrant or heterotopic pancreas
   Inflammatory pseudotumors

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Hamartomas and vascular tumors
Peutz-Jeghers' polyps/cysts

Collectively, benign tumors of the stomach make up less than 2% of all gastric neoplasms.

Most benign stomach tumors are discovered incidentally during laparotomy or in the course of diagnostic x-ray study of gastroscopy for unrelated disease. They usually appear in the fifth to seventh decade of life. Symptoms, when present, are usually the result of some complicaton, such as ulceration causing hemorrhage or intussusception through the pylorus, causing obstruction.

The principal clinical importance of these benign tumors lies in their relationship to malignant tumors. They must be differentiated from the malignant forms, an observation usually accomplished during laparotomy. Some benign tumors may also undergo malignant transformation. There have been reports of spontaneous disappearance of gastric polyps (2).

The management of such lesions has undergone some changes in recent years. With the advent of the endoscope and the experience gained by some operators, these lesions can be successfully removed by this method provided they measure less than 2 cm, are polypoid rather than sessile, and are not multiple.

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Senile Macular Degeneration and Kuhnt-Junius Degeneration as Separate Entities: Review

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Abstract

Senile macular degeneration and Kuhnt-Junius degeneration are both major causes of legal blindness in this country. These two diseases have in the past been thought of as actually different evolutionary stages of the same disease. However, the pathologic processes are entirely dissimilar. Histopathology of documented cases shows the existence of two distinct diseases.

The classification of macular degeneration should be based on histology and pathogenesis. Recent controversy has blurred the distinction between senile macular degeneration and senile disciform macular degeneration. Some authors propose a single pathogenesis and argue that both entities are stages in the progression of the same disease. Even though gross clinical examination and epidemiology are similar in some ways, senile disciform and senile macular degeneration are two distinct diseases.

The Role of Aging. Macular degeneration has been attributed to a disorder of the choriocapillaris, retinal pigment epithelium, and Bruch's membrane. One must understand the normal physiology and the aging process to understand the site and progression of the pathology. This is not to say that aging is the universal cause of such pathology, but rather that the mechanisms may apply in both circumstances.

Changes in the macula occur as a person ages. Metabolic waste accumulates in the retinal pigment epithelium, altered collagenous fibers increase in Bruch's membrane, and vessel changes can be seen in the choroid. It is unclear at what point changes due to aging signal the beginning of pathology. The age-related changes in Bruch's membrane include thickening and hyalinization, increased periodic acid-Schiff positivity, and basophilic staining. Garner attributes the thickening to the accumulation of plasma constituents owing to excessive permeability of the choriocapillaris endothelium (1). Hogan believes that the gradual decline in the metabolic activity of the retinal pigment epithelium leads to the accumulation of metabolic waste in Bruch's membrane and thereby decreases its permeability (2).

The pigment epithelium, lying just anterior to Bruch's membrane, serves as a conduit for nutrition from the choriocapillaris to the outer layers of the retinal neuroepithelium. Other functions include storage of vitamin A, manufacture of some of the mucoproteins that encase the outer and inner segments of the photoreceptors, and phagocytosis and digestion of the rod outer segment discs and other substances from the neuroretina. Since the pigment epithelium is such a metabolically active tissue, a great amount of stress is placed on it. It is therefore more subject to pathology when only minor changes occur.

Drusen. When the pigment epithelium performs the function of phagocytosis, lipofuscin pro-

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Written while ML, a third-year medical student at Downstate Medical Center, was participating in clinical research under the direction of GMG of the Department of Ophthalmology, Brooklyn (NY) Veterans Administration Hospital; while HL was a first-year intern in medicine at Beth Israel Medical Center; and while LJL was a third-year resident in obstetrics-gynecology at Beth Israel Medical Center, New York, N.Y.

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gressively accumulates in these cells. In addition, bodies of digested material gather and pass into Bruch's membrane, frequently into the inner portion. The deposition may be diffuse in the inner collagenous zone, or it may form discrete masses known as drusen. It is important to note at this point that drusen represent retinal pigment epithelium degeneration, no matter what the etiology is. Some authors argue that Kuhnt-Junius degeneration, another name for senile disciform degeneration, and senile macular degeneration are indeed one disease, as drusen occur in both pathologies. This logic implies that histologic markings represent a similar pathogenesis or similar disease. However, drusen are not pathognomonic of disease entities. Retinal pigment epithelium degeneration through whatever process can produce the same deposits.

The choriocapillaris is also subject to aging changes. The most extensive work in this area was done by Kerschbaumer in 1892 (3). To this day his description of these changes has been only slightly modified. The senile choriocapillaris exhibits loss of cellularity, thickening and hyalinization of the capillary wall, and depostion of PAS-positive sudanophilic material between the capillaries and Bruch's membrane. In addition, atrophic zones are found in the choriocapillaris which were topographically related to large choroidal vessels. It is important to remember that these changes were discovered in histology slides of normal senile eyes.

Both macular degenerations in question show physical similarities to the aging process. Macular degeneration occurring secondary to serous and hemorrhagic detachment of the retinal pigment epithelium from underlying choroidal disease is most commonly referred to as disciform macular degeneration. The term was first used by Oeller (4) in 1905 and later by Junius and Kuhnt to describe macular lesions in the elderly (5). It is a choroidal disease involving primarily degenerative changes in the choriocapillaris and Bruch's membrane, with secondary alterations in the pigment epithelium and retina. The various stages of evolution in this disease are serous detachment, hemorrhagic detachment and reparative stage.

The Evolution of Disease. An appreciation of the anatomy and vasculature of the area is necessary to understanding the evolution of disease. Bruch's membrane, composed of collagen and elastic tissue, forms the innermost portion of the choroid and is an intimate part of the stroma surrounding the walls of the vasculature—it is not a physically separate layer from the choriocapillaris bed. Its inner portion, an integral part of the pigment epithelium's membrane, provides a very firm attachment between itself and the pigment epithelium. The pigment epithelium is a monocellular tissue membrane that is not easily disrupted. However, unlike the Bruch's-pigment connection, the pigment-retinal layer is only a tenuous adhesion.

Any one of many disease processes can affect the choroid in producing localized areas of increased permeability of the choriocapillaris. This will allow a serous exudate through Bruch's membrane into the subpigment epithelial space. Only a very small detachment of the pigment epithelium can form owing to the strong Bruch's-pigment connection. This serous detachment of the pigment epithelium is usually a round, sharply circumscibed lesion. There are usually discrete deposits, drusen, adherent to the posterior surface. Shortly afterward, the subpigment epithelial fluid may move into the subretinal space. This is a less well-circumscribed area than the original serous exudate because of the greater ease in creating a space between the pigment epithelium and the retina. At this point, vision may remain normal for an extended period of time. In fact, if the original choroidal disease subsides, the neuroepithelium may reattach.

Now the disease may proceed to the hemorrhagic stage, in which there is a predilection for capillary proliferation from the choriocapillaris to pass through defects in Bruch's membrane. This blood supply stems from the larger choroidal capillaries rather than from the neighboring choriocapillaris tissue that was largely replaced by intercapillary stroma. Similarly as in serous exudation, blood will dissect its way through into subretinal space. However, as serous exudation is a relatively benign occurrence, hemorrhagic detachment causes irreversible damage. Blood may also find its way into the overlying retina and eventually proceed through into the retina. The seepage of blood in this process is most probably due to an ingrowth of new capillaries into the subpigment epithelial space. There is evidence that this space is supplied by choroidal vessels lying external to degenerated choriocapillaris. Since degenerating choriocapillaris deprives nourishment to the overlying outer retinal layers, neovascularization may be the body's attempt to replenish nutrition.

Reparative stages include degradation and resorption of blood in both the subpigmental and subretinal spaces. At the same time, fibrovascular proliferation from the choroid and metaplasia of the pigment epithelium lead to organization.

It is important to understand the vasculature of the eye as neovascularization has been shown to be an important part of senile disciform degeneration. The preferential location of the macula is used as evidence for the existence of one disease common to the pathological processes in question. Actually, the macula has a predilection because of the special circumstances in its vasculature. In the macula, a large volume of blood goes through the choroidal circulation by way of the short ciliary arteries. These arteries form an anastomatic network that empties into a sinusoidal complex of the choriocapillaris. From there the blood is drained by venous channels into the vortex veins. Such a concentration in this area accounts for a greater hemodynamic stress on the choriocapillary bed than in any other part of the eye. It is easy, then, to make the assumption that a disease dependent on the integrity of the choriocapillaris will most likely show up preferentially in the macular region.

Normal and Diseased Retinal Aging. The aging process seems intimately involved in the pathogenesis of senile macular degeneration as the retina changes. However, this degeneration is not an inevitable result of aging. Definite alterations in the retina differ from normal aging.

Senile macular degeneration has been described in the literature as a "dry" degenerative process of the retinal pigment epithelium and outer retinal layers. Habb in 1885 described the disease as a degeneration without neovascularization and as a choroidal sclerosis (6). Sorsby described it as a heredodegenerative disease (7). This last "dry" degeneration is typically seen as a macular defect of the neuroepithelium, retinal pigment epithelium, and of the choriocapillaris. This is a very well-demarcated atrophic area where all the capillaries and medium-sized vessels have disappeared. Neither these nor the observable posterior ciliary arteries are sclerosed. No breaks in Bruch's membrane were ever found, even though all the other layers were totally atrophic.

Another type of senile macular degeneration is associated with aging changes. As noted before, normal physiology wears out the integrity of the eye. Aging changes occur in the intercapillary connective tissue and include alterations of Bruch's membrane without fragmentation. In a documented case of a 104-year-old woman who gradually lost her vision to the point of legal blindness, histopathologic study showed marked degeneration of the outer retinal layers (8). Neuroepithelial destruction was not uniform. The cuticular portion of Bruch's membrane was thick and granular throughout the macula. The elastic portion was completely intact whereas the intercapillary stroma had considerably thickened.

As stated above, thickening of intercapillary connective tissue is a prominent part of senile macular degeneration. It is also found in aged eyes; however, aging does not necessarily produce it. The proportion found in such histology is far from an advanced degree of aging. This alteration of the intercapillary tissue, taking place very slowly, impedes the normal movement of nutritive solutions to the outer retinal layers. Diffusion problems will result in accumulation of materials on one side and deficiencies on the other side. Again, the presence of drusen will become evident.

Comparisons in histopathology make it clear that senile disciform degeneration and senile macular degeneration are two different diseases with two different pathogeneses. First, it is assumed that if subretinal neovascularization is merely an end stage of "dry" degeneration, then severe pathology should be present in the outer retinal layers and pigment epithelium. This would mean a progression has taken place, but this is not the case.

Green and Key reported 34 separate cases of what they considered to be senile macular degeneration (9). In one documented case, both eyes of an 87-year-old white man had drusen in the posterior pole (9). In addition, there was subretinal pigment neovascularization and an intact retinal pigment epithelium in the left eye. This then shows that drusen were not the primary result associated with pigment epithelium degeneration, but rather that another process had to be at work. If another process were not at work, it would be impossible to have drusen without a deteriorated pigment epithelium.

Another documented case is of an 88-year-old woman who showed serous detachment between the inner and outer portion of Bruch's membrane (9). The most important point to note is that a pathologic feature of senile disciform degeneration was present, the retinal pigment epithelium being fully intact. This coexistence cannot be explained by a single-disease theory.

Another patient, a 76-year-old white man, was diagnosed as having senile macular degeneration (9). He had extensive subretinal pigment epithelial neovascularization. Choroidal vessels were entering through a single break in Bruch's membrane, but the overlying pigment epithelium and photoreceptor layer were completely intact. This clearly describes an eye that has pathology in the choroid only, leaving the retina free of all disease. A single-disease theory could not explain this histology.

Kuhnt-Junius disease, otherwise known as senile disciform degeneration, is a separate pathologic process from senile macular degeneration. There are similar predispositions to the elderly and to the macular area, but this is common to all diseases that share aging mechanisms and are dependent on the special vasculature of the macula. Also, there is the common existence of drusen, which is no more than a result of some other primary disturbance in the tissue. Finally, these common findings become much less meaningful when studied histologically. This determines that there are indeed two separate diseases.

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Coombs' Positive Hemolytic Anemia Following Sulfasalazine Therapy in Ulcerative Colitis: Case Reports, Review, and Discussion of Pathogenesis

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Ulcerative colitis is an uncommon inflammatory disease involving colonic mucosa and submucosa. It is an idiopathic nonspecific disorder associated with various defects in the immune system. Reported here are two cases in which positive direct-Coombs' (autoimmune) hemolytic anemia (AIHA) developed following sulfasalazine (salicylazosulfapyridine; SASP) treatment for UC. A review of the literature is presented, followed by a discussion of the possible pathogenesis of this condition.

Case Reports

Case 1. A 33-year-old man was admitted to the hospital with multiple attacks of biliary colic. He was in his usual state of good health until five years prior to admission, when he began having episodes of bloody diarrhea. Colitis was diagnosed by lower gastrointestinal series and initially treated with SASP. Approximately two weeks after the start of SASP therapy, he developed painful limbs, hives, puffy facies, and fever. SASP was discontinued. His colitis subsided with a diet consisting of boiled and whole-grain foodstuffs. Four years later, he became jaundiced and had shortness of breath, fatigue, and pain in his groin. A diagnosis of hemolytic anemia was made and he was treated with prednisone, 80 mg a day. Two months prior to admission, he experienced repeated bouts of anemia. His hemoglobin was 4.7 g, hematocrit 14.6%, haptoglobin 22 mg/dl and the direct-Coombs' test was moderately to weakly positive for IgG, IgA, IgM, C3, and C4. The serum iron was elevated to 175 μg/dl (normal 80–160) and total iron binding capacity abnormally decreased 224 μg/dl (normal 250–400). Splenectomy was recommended at this time. One week prior to admission, following an episode of shortness of breath, severe epigastric pain radiating to his right back, and abdominal cramps, a sonogram revealed multiple gallstones.

On admission, physical examination was unremarkable. SMA-6 and SMA-12 as well as CBC were all within normal limits with a platelet count of 190,000. Splenectomy and cholecystectomy were performed without complications and postoperatively, the patient did well. The pathology report showed "a hyperplastic spleen with decreased lymphoid follicles, hyperplasia of sinusoidal lining cells, and trapping of red blood cells in the splenic cords consistent with hemolytic anemia." The gallbladder revealed "mild chronic cholecystitis, cholelithiasis, and focal cholesterolosis." One day postoperatively, his hemoglobin was 13.5 g, hematocrit 41.3%, and platelets 253,000. A direct-Coombs' test was moderately positive for IgG, IgA, IgM, C3, and C4 one week after surgery. Three months postoperatively, the patient was off steroid treatment and asymptomatic. The hemoglobin was stable at 14.0 g.

Case 2. A 40-year-old woman was admitted to the hospital with a chief complaint of bloody diarrhea, cramps, and chills of sudden onset. She was in her usual state of good health until four years before admission when, during a vacation in Mexico, she had severe episodes of abdominal pain, rectal bleeding, and up to 15 bowel movements a day. Upon return to the United States, a diagnosis of ulcerative colitis was made by colon-

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Written when the author was a third-year student at the Mount Sinai School of Medicine (CVNY). Address reprint requests to the author at the Department of Internal Medicine, Baylor College of Medicine, 6535 Fannin (B501), Houston, TX 77030.

oscopy and she was initially treated with cortisone and SASP, 3 grams a day, which provided relief.

On admission, her haptoglobin was 21 mg/dl, antinuclear antibodies were positive, and a direct-Coombs' test was strongly positive for IgG and weakly positive for C3b, C3d, C4, C, and c antigens. She was treated with ampicillin, 6-mercaptopurine, cortisone, and SASP, without relief. SASP was discontinued but six days later she developed toxic megacolon secondary to fulminating ulcerative colitis. A subtotal colectomy and ileostomy were performed. The pathology of the resected colon showed "massive necrosis, multiple ulcerations, and pseudopolyps." Postoperatively, the patient had an anemic episode along with wound infection and a pulmonary embolus. One month later, she had an intestinal obstruction with acute abdominal pain for 4–8 hours that resolved spontaneously.

Literature Review

A review of the English-language literature has revealed 21 cases of direct-Coombs' positive hemolytic anemia in association with UC but before any treatment with SASP (1–10). In three cases, the hemolytic episodes developed after colectomy was performed (4, 8). In two of these three cases the rectal stump was removed prior to onset of hemolytic episodes (8).

Ten cases have been reported in which direct-Coombs' positive hemolytic anemia occurred only after SASP treatment for UC. Balint et al (11) described a case of a 31-year-old woman with chronic UC, rheumatic heart disease, and diabetes mellitus who was treated for diarrhea and fever with 4 grams a day of SASP for five days without relief. Prednisone, 60 mg daily in divided doses, was begun after discontinuation of the SASP but within 9 days when the hematocrit began to fall to 30%, a blood transfusion was given. Cross matching at that time was difficult due to a positive direct-Coombs' test.

In another report, Fong et al (12) describe a case of a 35-year-old woman with a 6-year history of UC treated for severe bloody mucoid diarrhea with ACTH, antibiotics, and then SASP without relief. A total colectomy was performed during which the patient received 9 units of blood without transfusion reaction. Three years after the surgery, the patient was found to have a strongly positive direct-Coombs' test.

Black et al (13) report a case of a 23-year-old postpartum woman with UC initially treated with SASP and prednisone enemas. Two years later, the direct-Coombs' test was positive and the gammaglobulin neutralization test demonstrated "warm" antibodies with a predominantly anti-e antigen specificity (suggestive of autoimmunity).

Three cases presented by Bardana and Pirofsky (5) demonstrated direct-Coombs' positive hemolytic anemia following SASP administration. SASP was unsuccessful in controlling bloody diarrhea and malaise in two of these cases. Autopsy of one case revealed multinodular thyroid disease, bilateral ovarian cysts, and necrotizing pneumonia.

Arner et al (14) reported improvement of UC with SASP therapy in which three years afterward, diarrhea, anemia, reticulocytosis, and a positive direct-Coombs' test developed.

At The Mount Sinai Hospital of New York, two cases of UC were reported by Altman et al (10) in which good control of colitis with SASP treatment was observed. In one of the cases, transient episodes of erythema nodosum, arthritis, and severe headaches four years later necessitated discontinuation of the drug. This was shortly followed by demonstration of reticulocytosis and a positive direct-Coombs' test. In the other case by Altman et al (10), hypochromic microcytic iron-deficiency anemia developed during SASP treatment. SASP was subsequently discontinued and parenteral hydrocortisone, 300 mg a day, was begun. The hematocrit fell to 31% and with no improvement after a week, ACTH, 120 units a day, was substituted for the steroid. The hematocrit continued to fall to 21.5% and a positive direct-Coombs' test was demonstrated.

Most recently, Bell et al (15) reported a case of a 22-year-old man with UC whose symptoms rapidly ameliorated with SASP. Maintenance dosage was increased from 1 to 4 grams a day over a four day period to manage relapses until anorexia developed. The direct-Coombs' test was positive shortly afterward.

Discussion

Ulcerative colitis (UC) is a disorder associated with various immunologic aberrations such as AIHA (1), arthritis, spondylitis, iritis, erythema nodosum (13), necrotizing angiitis (16), scleroderma (17), systemic lupus erythematosis, pericholangitic and lupoid hepatitis (18), thyroiditis (19), Sjögren's disease (20), glomerulonephritis, myasthenia gravis (21), and microangiopathic hemolytic anemia (22).

Autoantibodies to colon, liver, kidney, and erythrocytes have been identified in UC (12, 23). Broberger and Perlmann (23) demonstrated positive precipitin reactions in sera from 22 out of 30 children with UC with extracts of heterologous human colonic glands obtained at colectomy. In two children with UC, hemagglutinating antibodies were discovered in extracts of lymph nodes draining the involved colon (24). In UC, increased antibodies to the *Escherischia coli* 0:14 antigen were demonstrated by Perlmann et al (25). Broberger and Perlmann (23) have suggested that true autoantibody production could result from absorption of altered erythrocyte antigens through an ulcerated colon and be triggered by an infection.

Anemia frequently complicates UC due to blood loss, transfusions, steroid therapy, inadequate fluid balance, acute inflammation, or nutritional deficiency (4). A megaloblastic anemia can result from diminished intestinal absorption of folate or vitamin B_{12} whereas a dimorphic anemia can result from diminished intestinal absorption of iron and vitamin B_{12} (4). Lorber (1) first described AIHA in UC in four patients. AIHA in UC might occur from direct injury of erythrocytes, alteration of erythrocyte surface structure, or diseased colon having a hapten in common with erythrocytes (1). Alternatively, an underlying genetic predisposition to aberrant immunologic responses might exist in patients with both AIHA and UC. Bardana and Pirofsky (5) hypothesized a multisystem immunodeficiency disease in which AIHA and UC are only two components.

The current mode of treatment for UC consists of trials with steroids and SASP, and colectomy. Treatment with SASP for UC was originally described by Svartz (26). In a double-blind study by Dick (27), approximately 75% of patients with UC receiving a maintenance dose of 4–6 grams a day of SASP benefited with treatment based on sigmoidoscopic appearance and clinical state. SASP is formed when sulfapyridine is combined with 5-aminosalicylic acid by an azo linkage (figure). After oral administration, 10–15% of SASP is absorbed by the small intestine (28). Cleavage of the azo group occurs in the remaining SASP by colonic bacteria forming 5-aminosalicylic acid (5ASA), which is excreted in the feces, and sulfapyridine (SP), which is absorbed by the colon (28). SP is acetylated and conjugated by the liver and then excreted in the urine (28). It is the serum levels of SP that primarily account for the various side effects of SASP, especially in slow actylator individuals (29–31). Actions of SASP include lymphocyte cytotoxicity suppression (32), generalized anti-inflammation (33), reversal of colonic sodium and water secretion (34), and reduction of fecal clostridia and *E. coli* (35). In general, anti-inflammatory actions are due to 5ASA and antibiotic actions are due to SP. Side effects of SASP are summarized in Table 1.

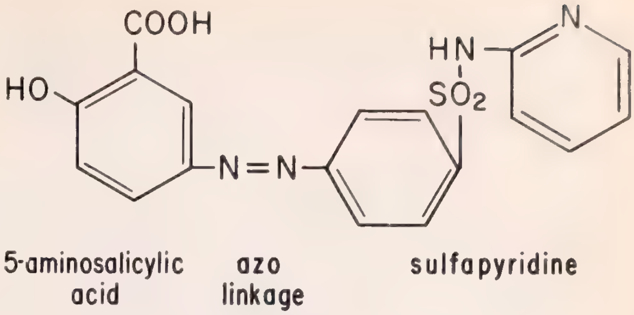

Fig. Sulfasalazine structure.

Summary

Cases have been presented that support the contention that AIHA associated with UC might occur via drug-induced autoantibody production. In the two cases reported here, AIHA did not occur until four years after initial SASP treatment. Autoantibodies in drug-induced hemolytic anemia are known to follow treatment with alpha-methyldopa, cephalothins, mefanamic acid, fuadin, and penicillin (8). Based on the temporal relationship between AIHA and SASP treatment, it is proposed that AIHA is a potential side effect of SASP therapy in the context of UC. In certain UC patients where the predisposition to AIHA is not great enough, SASP treatment might provide the necessary trigger for autoimmunologic stim-

TABLE 1
Side Effects of SASP

Generalized	Gastrointestinal	Hematologic
headache	nausea	nonautoimmune Heinz-body oxidative hemolytic anemia
vertigo	vomiting	leukopenia
skin rashes	anorexia	agranulocytosis
fever	abdominal discomfort	pancytopenia
joint reactions		transient reticulocytosis
nephrolithiasis		leukoagglutinin formation
cyanosis		

Adapted from Das KM, Eastwood MA, McManus JPA, Sircus W. Adverse reactions during salicylazosulfapyridine therapy and the relation with drug metabolism and acetylator phenotype. N Engl J Med 1973; 289:491–495; Svartz N. Salazopyrin, a new sulfanilamide preparation. Acta Med Scand 1942; 110:577–598; Moeschilin S, Meyer H, Israel LG, Tarrgloor E. Experimental agranulocytosis. Acta Haematol (Basel) 1954; 11:73–94; and Spriggs AI, Smith RS, Griffith H, Truelove SC. Heinz-body anemia due to salicylazosulphapyridine. Lancet 1958; 1:1039–1041.

ulation. This results in an eventual positive direct-Coombs' test, indicating the presence of autoantibodies to erythrocytes. Interestingly, in both cases reported here, the haptoglobin level was decreased, characteristic of drug-induced immunohemolytic anemias.

In short, one must be cautious when treating UC with SASP. Periodic hematologic studies, including CBC and direct-Coombs' test, should be performed. Any indication of predisposition for autoimmune complications, for example skin rashes, thyroiditis, or arthritis, should alert the physician to the possibility of subsequent SASP treatment causing an AIHA.

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Letters to the Editor

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Importance of the Lymphatic System

To the editor: It is perhaps unusual for an international society to feel it essential to draw attention to the very existence of its subject matter. However, such is the general lack of knowledge about the lymphatic system that the International Society for Lymphology believes that the following well-established points need reiterating:

1. All regions of the body are drained by the lymphatic system. Often the initial (terminal, capillary) lymphatics are joined to the most remote parts of the interstitium by tissue channels only a few tens of microns long, just as are the blood exchange vessels. In a few regions these channels form systems many cms long, but still drain into true initial lymphatics eventually. In the cases of the brain and retina they do this outside the skull. Except in edema or in encapsulated organs, fluid will normally only enter the initial lymphatics if there are variations in tissue pressure—caused by movements, contractions of adjacent muscles, etc. These also help propel the lymph in the large lymphatics, but intrinsic contractions in their walls also cause it to flow.
2. The lymphatic system removes a small proportion of the smaller molecules from the tissues, which is important in preventing edema. Some smaller macromolecules also pass to blood, but usually most (and certainly all the larger ones) are removed by the lymphatic system. (Some removal is by tissue proteolysis.)
3. The presence of any edema implies that the lymphatics (as well as the other mechanisms which act to prevent edema) have been overloaded. This may be because of an excessive lymphatic load with a normal system, or because of a normal load with a deficient system, or both.
4. If all the lymphatics draining a large region (e.g. a limb) are simultaneously completely obstructed, the animal dies within 1–3 weeks from loss of protein via lymphocutaneous fistulae. This does not happen in humans because such abrupt and complete lymphostasis does not occur.
5. The neglect of lymphatic transport can cause considerable errors in physiological experiments on the blood microcirculation.
6. In clinical practice, while edemas near the surface are often observed, many of those of deeper organs are not.
7. Edematous tissues have poor oxygenation, considerably reduced functional capacities, and heal slowly. A chronic high-protein edema is one cause of chronic inflammation and fibrosis.
8. Any interference with lymphatic transport can provoke a lymphedema—especially if the system is deficient or overloaded. This may be as insignificant as an insect-bite. Iatrogenic damage includes the removal of lymph nodes, lymphangiography (with media which damage lymphatic walls), excessive radiation, inappropriate surgical procedures damaging lymphatic trunks, which often lie adjacent to the large blood vessels. Sometimes special considerations make it essential to perform such procedures, but it must be realised that they may provoke lymphedema.
9. Lymphedema can now be prevented or treated, and sometimes completely cured, by a number of methods. It is no longer ethical to neglect it. As in all high-protein edemas, diuretics are contraindicated except in emergencies, or for coexisting diseases.
10. The objects of the International Society for Lymphology are to promote knowledge about the lymphatic system: its structure and function, its investigation in patients, the treatment of its deficiencies and its roles in immunology and neoplasia, etc. Information about this body and a list of books and reviews on the lymphatic system may be obtained from The Secretary General, I.S.L., Tullastrasse 72, D-78 Freiburg, West Germany.

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Letters to the Editor: Letters should be short and will be subject to editing. Objective, constructive criticism of published articles or discussions of questions of general interest in medicine are welcome. Double-space the text of the letter and any accompanying references or tables.

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Health Services and Social Research: The Bridge Between

Jane Zech Moss, Ph.D., and Renate Belville, M.A.,
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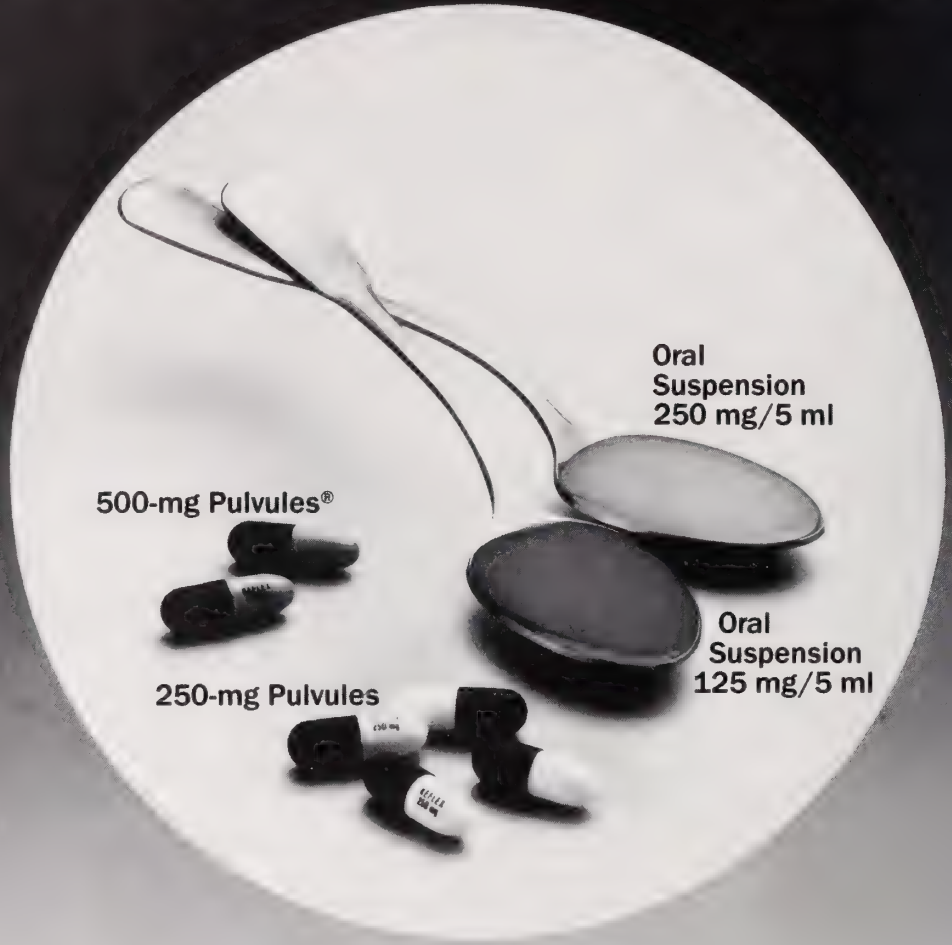
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CONTENTS

HEALTH SERVICES AND SOCIAL RESEARCH: THE BRIDGE BETWEEN

Introduction *Jane Zech Moss, Ph.D., and Renate Belville, M.A.* 672

BASIC ISSUES

A Perspective: Health Services Research at The Mount Sinai Medical Center *Kurt W. Deuschle, M.D.* 677

Basic Research and Its Potentials of Relevance *Robert K. Merton, Ph.D., adapted by Jane Zech Moss, Ph.D.* 679

What We Don't Know about Why Health Expenditures Have Soared: Interaction of Insurance and Technology *John Goddeeris, Ph.D., and Burton A. Weisbrod, Ph.D.* 685

CASE STUDIES

Health Services Research for Hospital Policy *Jane Zech Moss, Ph.D, and Renate Belville, M.A.* 693

Health Services Research in Action: Explaining a Decrease in Patient Visits at a Diabetes Clinic *Renate Belville, M.A., David Florman, M.B.A., and Charles Nechemias, M.D.* 702

Evaluating a Proposed Change in a Delivery System and Reimbursement Structure: A Case Study of Planning for a Hospital *Raymond K. Cornbill, M.B.A., Peggy Foner, M.P.H., and Deborah E. Halper, M.P.H., M. Sup.* 708

Development and Application of a Productivity Data Base for Hospitals *C. Douglas Kundel, B.S.* 714

continued

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CONTENTS *continued*

Constraints in the Development of a Rural Primary Health Care Program in the Dominican Republic *Ellen Fischer, M.P.A., and Rolando Merino, M.D.* 719

The Role of Social Scientists in Planning and Implementing Change in a Medical Center *Renate Belville, M.A., and Jane Zech Moss, Ph.D.* 724

COMMUNICATING AND DISSEMINATING RESULTS

Research Settings and Health Services Research: Does Where You Do It Affect Who Listens? *Geoffrey Gibson, Ph.D.* 731

Seminars for Congressional Aides: An Educational Program on the Role of the Urban Academic Medical Center *James F. Glenn, M.D., John T. Grupenhoff, Ph.D., and Patricia S. Levinson* 736

The Role of Research When a Biomedical Issue Is Politicized: The Regulation of Methadone Maintenance Programs *Rogelio I. Thomas, M.D., M.P.P., and Claude J. Aguillaume, M.D., M.P.H.* 740

Can Academic Medical Center Health Services Research Be Useful in Community Development? *Samuel J. Bosch, M.D., Roland Merino, M.D., M.P.H., David Rose, M.D., and Kurt Deuschle, M.D.* 744

Arbitrating Change in Staff Attitudes and Training Programs on a Surgical Service *Madeleine Mathiot, Ph.D., and James S. Williams, M.D.* 749

Health Services Research in Aging: What We Need to Know *Michael McCally M.D., Ph.D., and Christine Cassel, M.D.* 753

Index to Volume 52 758

Index to Advertisers

Eli Lilly and Company	**cover 2**

The Mount Sinai Journal of Medicine
Vol. 52, No. 9, November 1985
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Health Services and Social Research: The Bridge Between

Introduction

Jane Zech Moss, Ph.D., and Renate Belville, M.A.

During the 1960s health services research became a separate area of study. It was born and flourished in response to the need for information of executives and administrators operating newly created centralized national agencies. These Great Society agencies were created to finance and develop new forms of health services delivery, the first such attempt in the United States. Previously, health care had been a local responsibility, resting with the individual, the family, the municipality, or the county.

As administrators, the new national staff needed to know the effectiveness of each program, as distinct from its efficiency—the social impact as well as the economic impact. It is the study of the social impact of programs on which we are focusing in this collection of essays. In the flood of newly created Great Society programs, such an extensive amount of research was commissioned that in 1966 the National Center for Health Services Research was founded to coordinate and direct the various research enterprises.

By 1985, the central administrators and other staff who had commissioned research had voiced their doubts about the usefulness of many of the completed studies. Researchers, in turn, were both defensive and self-questioning. Numerous articles appeared in professional journals presenting arguments on what factors accounted for this presumed lack of utility and why. New journals were established to address issues of utility; one, for instance, focusing specifically on utilization, was called *Knowledge: Creation, Diffusion, Utilization* (Sage Publications, Los Angeles).

Because the new federal agencies were not getting the results they needed, they began to replace simple, unstructured government grants with contracts in which the commissioning agency stated its explicit specifications for the research to be supported. Independent academic researchers were, as a result, more likely to restrict their activities to collecting data from an explicitly defined sample and less likely to be designing and interpreting their own data. After twenty years of experience, many operating agencies in Washington had their own in-house research units, and less research was commissioned from the universities. What happened during the twenty years from 1965 to 1985 to account for the broad failure in the utility of health services research?

In his 1980 review of health services research and its critics, Bice reports a general consensus among administrators that, although research findings were incorporated into the general thinking about health services delivery, the particular instrumental kind of research directed to the problems of the administrator had failed. He states:

> Those who lament the poor record of health services research as an instrument of forming public policy lay blame primarily on the researchers and their styles of work and communication. . . . Social scientists are accused of remaining aloof from the realms of practical and political affairs, shielded by their doctrines of value neutrality and disciplinary purity. Further, they are charged with lacking sufficient insight into real-world needs and the routines of policy makers and of failing to take proper account of these in their conceptualization and communication of research (1).

From the Office of Applied Social Research, Department of Community Medicine, Mount Sinai Medical Center, Suite 9D, 19E. 98th Street, New York, NY 10029. Address reprint requests to the author there.

To understand how some of this occurred, it is useful to see how the context of the research has changed. Prior to the 1960s, although many kinds of social research were carried out, the die cast by the dominant Columbia school in New York governed the research approach for sociologists (2). This approach had developed in response to the need of manufacturers and advertisers to know the effects of mass communication in the mass media on a pluralistic national public. The client wanted to know which groups a campaign or program reached and how these groups were affected by the communication. From the research the client was informed how the social characteristics of the audience reached—for instance socioeconomic status, educational level, membership in networks of friends and in channels of communication—affected the impact of the program or campaign.

When in the 1960s social researchers turned to health services research, both the problems and the clients were different. The mass audience could be studied by concepts and methods then available within the discipline of sociology. But the same approach was not applicable to programs in health care. Another kind of research approach was needed, more amenable to understanding how a new program works, for whom, and how it can be changed to work better.

Coleman (3) has articulated a basic distinction between "discipline research" and "policy research." Discipline research is designed to provide information or knowledge in support, modification, or rejection of social theory. Policy research is designed to provide information for action. Health services research is a particular substantive area for policy research, and the kind of research needed is evaluation.

The response from researchers to changes in the nature of the problem to be researched has been to pursue several different kinds of evaluative research. These were named for the level of feedback to which they were directed: formative, summative, and process evaluation. "Formative" or "concurrent" evaluation was intended to provide information to a program manager for concurrent modification and program improvement.

"Summative" evaluation focused on the end results, the outcomes or effects of a program, and was generally designed to answer questions at a higher level than that of the manager. These evaluations were often used to inform the debate of decision makers over broad areas of public policy. Studies on experimental medical care programs, for instance, or on HMOs as a form of service delivery, are examples of this kind of evaluation.

Another and more recent type of evaluation research is that of "process" evaluation. Here the use of resources in the course of delivering a program is the focus of the study. This more recent kind of research comes from a methodological predecessor found in organizational research rather than from the survey method used to study audiences, the earliest prototype for most policy research.

These three types of evaluative research developed in response to the differing levels of program responsibility in organizations. They do not yet fully cope with the interaction between organization and environment, or with interaction within organizations.

In evaluative research, the response to the client and the client's organizational context has been less well developed than the response to the problem under study. The "action" possible to the client will differ with the level of policy responsibility within the organization borne by the client and the variables for changes that are available to him or her. Policy is made at all levels in an organization or institutional order. Only the available means, scope, and jurisdictions change. The "action" available to the manufacturer and the advertiser is the widest possible. They can determine the kind of message they create for and present to an audience. They can determine how it is presented, when it is presented, and where it is presented. In health services, on the contrary, the possible response of the research client is limited, partial, and fragmented—the extent of the limits depending always on the client's position in the organization, the mandate of the organization, and the time requirements for decision.

Between the administrator in the federal office and the public who are the recipients of the new delivery systems for health care services lie very complex intervening variables. These are located in the organization: the program, the neighborhood health center, or the hospital. Health care services or resources are delivered by administrative delegation through a complex organization. Within every organization lie interrelated variables involving various professional and nonprofessional staff groups and organizational processes, as well as different populations of recipients of service.

Depending on the level of administration borne by the client, the nature of the variables affecting policy-making and change vary. In the central federal agency, the administrator might make policy about the eligibility of persons to be served, standards to be met, or neighborhood characteristics in the area where the service is to be established. The central office can promulgate regulations, and ultimately the administrator at this level can determine to support or cease to support a particular health care agency. But the variables available for change are limited.

At another level, that of the program director, it is possible to change the structure of work, schedules, procedures, staffing, and coordination. At the level of the first line—those staff members in immediate contact with patients, including receptionists, transporters, nurses, social workers, and physicians—it is possible to change the approach of any group of staff to the patient by changing the mode of communication or some aspect of the encounter with the patient. In each case, the variables are limited and to some extent dependent on the level of cooperation and resources available from the organizational level above. A physician might, for example, try a new or alternative kind of explanation to a patient in hopes of better compliance. If the explanation requires too much time and a queue of patients forms, a new problem has been created. At each level, the variables available for change are limited.

Too often, the researcher has not known the routines, the problems, the bottlenecks, the shortages, the staffing problems and skill levels, the politics, the values, and the priorities within the organization being studied, or the impact of these factors on the outcome of service for the patient.

Policy makers and administrators do face a "real world" in which they require feedback on matters other than and in addition to the direct effects of a policy. The policy itself fits into a larger context. It competes with other policies for support and for resources. It has economic and political consequences. These factors, which can be numerous, are at least as important, and sometimes more important, than the direct effectiveness of a policy in decisions to implement or continue a program or some part of it. Knowing what the effectiveness of a program is, is not sufficient for decision making; all the factors that bear on feasibility need to be considered in recommendations formulated by the researcher.

Looking for clues to some of the issues raised in formulating problems and understanding clients, we have focused in this collection of essays on the themes of relevance and application of research findings. We have grouped the essays into three sections.

Section 1: Basic Issues. The articles in the first section address the issues of relevance and interrelatedness of concepts.

To begin, Deuschle offers us a perspective on the field of health services research and the role of the Department of Community Medicine at The Mount Sinai Medical Center, New York, in ongoing health services research efforts.

In "Basic Research and Its Potentials of Relevance," Merton discusses the usefulness of findings from basic research and their applicability for human use. He strongly supports the intrinsic value of research as a pure quest for knowledge in and of itself, permitting the independent investigator free reign of intellect and imagination. It is a time-honored academic tradition.

Goddeeris and Weisbrod examine the mainstreams of economic research in health services and suggest that it is necessary to step out of the mainstream and examine the direction of research efforts. In doing so, they suggest new ways of relating two different streams of contemporary economic research that may offer results more realistic or more applicable than current unidirectional work provides.

Section 2: Case Studies. The second section in this collection of essays is devoted to case studies in application. Moss and Belville describe policy research in a hospital, seen as an organization. They develop a paradigm distinguishing four types of organizational stress that constrain researchers within an organization, and the research they can accomplish—illustrated by a case study of a research project—under each sort of constraint. Such constraints can be minimized with cumulative knowledge of the organization and data bases. Clarity, flexibility, and organizational appropriateness are the overriding considerations in answering the need for organizational action.

In "Health Services Research in Action," Belville, Florman, and Nechemias describe a question that arose with respect to the interpretation of events in a hospital clinic, namely, a reduction in patient visits. The study develops step by step as the authors pursue a clarification and interpretation of the phenomenon.

In the article that follows, Cornbill, Foner, and Halper describe the issues presented to a medical center when an experimental Medicaid reimbursement system was proposed by the city administration. The authors describe the organizational process: appointing a committee with appropriate membership, articulating the various alternatives for response, and evaluating the alternatives through the application of available data and professional judgment.

Kundel illustrates the application of an available data base, data collected to meet the requirements of the New York State hospital reimbursement system, to construct a tool which enables hospitals to evaluate different departments of their own hospitals by comparing their departments with similar departments in other hospitals.

Fischer describes problems encountered when findings from a population survey contradicted the planning that was done for a primary care health program in the Dominican Republic. She looks at some of the organizational and cultural problems confronted by the planners when they tried to implement their plan with local providers of health care.

Belville and Moss complete this section with their description of the interface between social research and organizational planning in the development of a hospital-based group practice. They illustrate how data available in the hospital's computerized system can be used to select an appropriate population for a new program.

Section 3: Communicating and Disseminating Results. The third and last section gathers together papers concerned with the communication and dissemination of knowledge gained by research. The section opens with Gibson's paper, which describes the advantages and disadvantages of different types of research settings for the application of findings in health services research. He examines a number of factors relevant to the effectiveness of health services research.

Glenn, Grupenhoff, and Levinson discuss the dissemination of information on the nature and workings of a tertiary medical center to congressional aides. The aides work for congressional representatives on committees charged with responsibility for federal policy on health care and health facilities. The focus is to assist the aides to a better understanding of the complexities in a large medical center, as an underpinning to their contribution to federal policy making.

Thomas and Aguillaume sketch out a broad view of impediments to further support of drug rehabilitation programs whose efficacy is established. Their focus is on the effects of different interest groups in inhibiting the dissemination of treatment.

Bosch, Merino, Rose, and Deuschle describe how the Department of Community Medicine at Mount Sinai School of Medicine (NY) moves outside the institution to help community decision makers plan and develop health care models and research projects to meet community needs.

Mathiot and Williams describe the use of anthropological techniques to elicit information from surgical residents with respect to their work as trainees, then use the information to structure discussions and extract from the discussions a staff consensus used in restructuring certain aspects of the training program for residents.

The concluding article is a comprehensive review by McCally and Cassell of research that is needed for the new discipline of geriatrics. These authors pinpoint unresolved issues in the care and treatment of older persons and ask that researchers address themselves to filling these realistic needs of an ever-growing segment of recipients of medical services.

The range of topics and issues in this collection is illustrative of the web of problems facing researchers in the field of health services research. These papers represent fragments in the pattern of development of research efforts. They are in the middle of the beginning.

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Basic Issues

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A Perspective: Health Services Research at Mount Sinai Medical Center, NY

KURT W. DEUSCHLE, M.D.

"Health services research is concerned with problems in the organization, staffing, financing, utilization, and evaluation of health services. This is in contrast to biomedical research, which is oriented to the etiology, diagnosis, and treatment of disease. Health services research subsumes both medical care and patient care research. It could well be termed socio-medical research" (1). It is the newest of the meta-medical sciences, having become a separate discipline in the 1960s (2). It was born at a time of social concern for improvement in the quality of, and access to, human services. This concern grew out of a new national consciousness that developed after World War II—a consciousness of inequality among our citizens in a time of prosperity and a new national role in world affairs. America "woke up" and demanded a democratic process for the allocation of national resources such as health care, education, and employment. The government responded and under Lyndon Johnson launched the largest series of domestic programs in our history.

The field of health services research was a response by social scientists to the need to evaluate these new programs. The field of community medicine was a response by the medical profession to the social needs brought to consciousness in the 1960s.

The founders of the Mount Sinai School of Medicine in New York wanted to create a school that would not only meet challenges of biomedical science but would also be responsive to the needs of their community. In line with this mission, a Department of Community Medicine was included in the plan for the medical school. Its goals were first, to articulate and develop means for a medical school to offer expertise to community groups in matters of health, particularly focused on environmental and occupational health problems, and second, to collaborate with community groups in the development and utilization of their own health services programs.

Since its beginning, the Department of Community Medicine has evolved an ongoing health services research agenda. Included in this agenda have been collaborative projects with the departments of medicine, pediatrics, geriatrics and human development, psychiatry, nursing, and surgery.

Each division of the department has conducted some aspect of health services research. The Division of Social Work has produced research on identified institutional problems affecting workers and patients. The Health Services Unit has worked with community groups to articulate the community's own needs and develop the community's own resources, and the Behavioral Science Division has promulgated discipline research in medical sociology. From the latter two divisions, the Office of Applied Social Research evolved as a separate but collaborative enterprise.

As the Department of Community Medicine forged its own mold and appropriate policies, support was offered by a multidisciplinary staff to community groups in carrying out the community's own health care agendas. Although citywide, state, national, and international technical assistance projects have been conducted by the department, major attention has been devoted to the East Harlem community in which the hospital and medical school operate. Part of this community development was the hospital itself—struggling for the integration of a new medical

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school with a hospital long established and prestigious for its clinical specialties. Sociologists involved in organizational research made the hospital their arena of research, thereby establishing the first in-house health services unit in a hospital—the Office of Applied Social Research in the Department of Community Medicine.

During the past 16 years, the Office of Applied Social Research has evolved an approach to the study of health services in the hospital seen as a highly specialized organization emphasizing the development of research and methods of knowledge dissemination applicable within the hospital and addressing current issues and problems.

As an in-house unit, the group has responded to changing issues as the internal organization of the hospital and demands from the organizational environment changed. The unit has established for the hospital an integrated historical data base on physicians and patients and their utilization of the hospital. The data base serves as a source of information for monitoring hospital activities and for numerous studies of policy issues.

The editors have assembled for this issue theoretical papers and studies from within the Medical Center and outside it to illustrate the wide-ranging areas in which health services research methodologies can be applied to define and help solve health care problems, both in institutional settings and in community groups. In view of the fact that the United States is in the throes of a health-care revolution, especially in the financing of health services, the need for health services researchers to address the salient issues will continue to be acute. The articles presented here are useful both in their findings and in their methodologies.

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Basic Research and Its Potentials of Relevance

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adapted by JANE ZECH MOSS, PH.D.

Abstract

This exploration of the differentiation of basic and applied research emphasizes three components: personal intent of the researcher, social role of the researcher, and cultural (that is, cognitive) consequences. This distinction, in turn, gives rise to a new way of looking at research in terms of its potentials of relevance for human interests other than knowledge itself, and suggests an evolving relationship between the academic and health care communities.

Science has become one of the dominating social institutions of our time, directly or indirectly affecting all our lives everywhere. A wider range of problems than ever before is now tackled from the perspectives of science. Through the technologies to which science occasionally gives rise, it has comprehensively changed the world in which we live and how we live in it, just as it now goes far toward determining when and how we shall die.

Legitimizing Science. The enterprise of science is now so widely accepted that we are apt to forget the long historical process through which it came to be accorded social and moral legitimacy. A short three centuries ago, the physical and biological sciences, and a while later, the social sciences, were much on trial. They were granted legitimacy not so much as values in their own right as by being linked with other values that were widely accepted. That is why efforts were made on every side to show that the new science served the purposes of God and organized religion, the needs of the economy and the military, and the material well-being of the population (1). As Galileo put it when he was under fire for his Copernican ideas, "I find it necessary to justify myself in the eyes of all men whose judgment in matters of religion and reputation I must hold in great esteem." Later, Robert Boyle found it advisable to argue for the practical value of the new science in his tract, symptomatically entitled "*Usefulness* of Experimental Natural Philosophy." The primary case for science was made by showing that it would help us achieve objectives other than knowledge itself: power, comfort or pecuniary gain, health, repute, efficiency, or almost anything other than knowledge itself.

"What Good Is a Newborn Baby?" In time, this dependence of science upon other institutionalized values began to change. Science gradually acquired an increasing degree of autonomy, claiming legitimacy as something good in its own right, just as much so as literature and the other arts, as the quest for physical well-being or for personal salvation. The new legitimacy is reflected in Ben Franklin's reply to the question put to him about the use of a new discovery: "What good is a newborn baby?"—a reply echoed by Pasteur and Faraday in the century to come. The attitude expresses a double confidence: that fundamental scientific knowledge is a self-contained good and that, in due course, it will lead to all manner of practical consequences serving the

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varied interests of humanity. There developed an intrinsic as well as a utilitarian rationale for basic science. As we shall see, these rationales are bridged by the "potentials of relevance" of basic scientific research for human interests other than knowledge itself.

The Components of Basic and Applied Research

The growth of science has invited debates over the distinctive character of basic or fundamental research and applied research and development. These dialogues seldom result in exact agreement on the meanings of the principal terms, just as they seldom result in such full disagreement as to preclude further dialogue. Rather than enter still another pair of definitions into the lists, I shall identify the bases of agreement at the core and of disagreements at the periphery of these concepts.

A Functional, Not a Motivational, Definition. Basic research discovers uniformities in nature and society and provides new understanding of them. This conception, it will be noted, departs from a prevailing tendency to define basic research in terms of the aims or intent of the investigators. It is a functional, not a motivational, definition. It refers to what basic research objectively accomplishes, not to the motivation or intent of those engaged in that research. To be sure, the intent of investigators will affect the actual conduct and outcome of the investigation: the aim to discover new understandings will make it more probable that the research will be fundamental rather than practical, just as an applied orientation will more often result in utilizing basic knowledge simply to achieve designated outcomes. Nevertheless, in the behavior of scientists, as with human behavior generally, subjective intent and objective consequence are analytically separate, coinciding at times and differing at times. Just as inquiries aimed at fundamental knowledge have repeatedly turned up unsuspected applications, so inquiries aimed at application have, though perhaps less often, turned up unsuspected understandings of uniformities in nature and society.

Applying the Definition. Abandoning the aim or intent of scientific inquiry as the exclusive criterion, we can distinguish applied research from basic as that which makes use of existing knowledge, fundamental or empirical, to achieve old practical outcomes in new ways, or, at times, wholly new outcomes. Basic and applied research are alike in developing new knowledge by drawing upon past knowledge. They differ in that the new knowledge developed by basic research is of a kind that adds to general understanding of uniformities that go beyond any particular class of applications; it adds to the intellectual capital that comprises scientific knowledge. Applied research draws upon that capital to arrive at new methods of achieving practical objectives that are themselves outside the sphere of basic knowledge.

Personal and Cultural Components. Intent can be loosely classified as the "personal" component in research and the actual cognitive consequences of investigation as the "cultural" component (the increments accruing to the stock of knowledge and implements that make up part of the scientific and technological culture).

Social Components. Apart from intent and consequences, a third order of component distinguishes basic from applied research. That component is the "social," referring to the social roles assigned those engaged in scientific research. The role of workers in basic research has distinctive characteristics: (a) it provides them with relative autonomy in selecting the problems on which they will work; (b) it gives them latitude for deciding to shift from these initial problems to others turning up in the course of the inquiry, which they find more interesting or promising; and (c) in this role, the primary "reference groups"—the individuals and groups whose appraisal of their work they regard as central—are made up primarily of fellow-scientists, nonscientists entering only at a distant remove. In describing these as elements of the social *role* of scientists engaged in basic research, I mean to emphasize that they have social grounds for claiming these as rights and that others tend to honor these claims. I do not mean to say that, in any concrete case, there is full agreement on these role-defined rights or that particular scientists are not exposed to strains when others exert pressure to have them depart from that role.

In all three aspects of the social component, the role of workers in applied research tends toward the other extreme: (a) although the investigator may at times select a problem, the choice tends to be constrained by the particular practical outcomes which others judge worth achieving; (b) once launched on the inquiry, the investigator is the more often expected to stay with it; and (c) to a far greater degree, the most significant judgments of the work are made by an institutionalized reference group comprised of people outside the field of science who are charged with responsibility for making practical use of the results.

The concrete arrays of scientific researches involve differing mixes of personal intent, social role, and cultural consequences. Although the three components are probably correlated, the extent of the correlation is unknown, with the possibility that a sizable minority of present-day research, varying perhaps by discipline, falls between the extremes of the pure type of basic research and the pure type of applied research.

Interdependence of Science and Other Social Institutions

The historical fact that science has become a major resource means that more than ever the other institutions of the society must take up some position—sometimes only by default—on their relations to science. This is only a special case of the general sociological premise that the institutional orders coexisting in a society—the family, economy, and polity, science, religion, education, and medical practice—are variously interdependent while each still has a measure of independence. Total social structures can be distinguished in part by the degree of independence accorded each institutional sphere, as we see by contrasting the polar extremes of a totalitarian and a free society.

Like other social institutions, science is a citadel of values and interests protecting the functions distinctive of that institution. The institutional role of scientists—like that of governmental officials, leaders of business, labor leaders, religious leaders, physicians, and educators—invites them to resist developments which they see as invading their sphere of autonomy, so that they lose in independence what they seem to gain from new forms of social support. For science, the core of autonomy is found principally in the scientists' commitment to basic research. This, as we have seen, is comprised in its pure form of the *personal intent* to search out new understandings of uniformities in nature and society, the *social role* assigned scientists to select their own problems for investigation and to follow their own bent in conducting that investigation, and the *cultural consequences* which enlarge fundamental knowledge, all apart from its serving other human purposes. Many scientists accord greater value to basic than to applied research not alone because of its function of extending fundamental knowledge but also because it symbolizes the distinctive claims to autonomy of science. Any policy governing the relations of science to other social institutions which fails to take account of this enduring quest for autonomy is apt to be self-defeating.

Interdependence with Independence. The relations between organizations for delivery of health care and basic scientific research can now be seen as a special case of the relations between two connected but independent types of social institutions. Policy governing these relations would do well to recognize this composite of interdependence and independence. It calls for arrangements that serve the distinctive interests of science and of health care which do not alienate large numbers of people in the ranks of the two groups. Under such arrangements, scientists engaged in basic research are not to be required to abandon their role-commitments by turning to applied and developmental research, just as the directors of medical organizations are not to be required to abandon obligations to their constituencies by supporting research that apparently has no conceivable bearing on the principal purposes of their organizations.

On this view, arrangements connecting health care delivery and basic science must be designed, so far as possible, to maintain simultaneously the integrity of basic research and the integrity of the service organization. That these diverse interests collide at the edge does not mean that they necessarily collide at the core. That, at least, is assumed by the concept of the potentials of relevance of basic research for diverse organizations and institutions.

Potentials of Relevance

The concept of the potentials of relevance directs attention to the obvious and important fact that different sectors of the spectrum of basic research have differing probabilities of being germane to current and future functions of various types of organizations. Applied to the case of health service organizations, the concept gives rise to the policy of supporting those lines of inquiry in basic research which, so far as can be judged, will have the greatest degree of relevance for the particular organization. (This is not in place of a policy of supporting applied and developmental research directed toward the solution of specific problems.)

The policy of supporting basic research with potentials of relevance has several interesting properties. First, it preserves a substantial freedom of choice of problems by scientists. This makes it more probable that they will be the more thoroughly committed to their research and that, through self-selection, they will be investigating problems which they are individually best equipped to deal with. The process of self-selection is of course not infallible; it does involve a margin of error in matching person and research problem. But, in the large, it is apt to summon the deepest motivations of investigators and to draw upon their distinctive skills and capacities.

Second, the policy preserves a substantial freedom of choice for supporting organizations—whether medical, labor, government, or voluntary association—to select from the spectrum of ongoing basic research those lines of inquiry that hold most promise of yielding new fundamental perspectives on their own activities and functions.

These two aspects of the policy can be summed up in a third: it provides for a negotiable relation between basic science and medical or other organizations that keeps each from tyrannizing over the other. They meet on the comparatively neutral ground in which each retains its central commitments while allowing for a degree of mutual gain.

Fourth, it is evident that a prevailing policy of support for basic research having maximum potentials of relevance for each kind of supporting institution will, in the aggregate, make for selective apportionment of resources for many, but not all, kinds of basic research. There is no invisible hand at work to ensure that every type of research will receive support. Imbalances are bound to develop; certain types of basic science will have great practical potentials for key industries, other sectors of practice will receive a good deal of support, and still others will receive very little.

This leads directly to a fifth observation: basic science which has little potential of relevance for the purposes of organizations, in and out of government, is precisely the kind that needs to receive its primary support from institutions which have evolved to help advance basic knowledge, all apart from anticipated practical outcomes. Over the long run, the major institution evolving to support this kind of basic science has of course been the university. More recently, another type of institution able, though not always ready, to serve the same function of supporting scientific inquiries with little potential of "practical" relevance is the great private foundation. And, finally, such governmental establishments as the National Institutes of Health, the National Science Foundation, and sectors of other governmental agencies supporting scientific research have helped to fill in the interstices in those sciences which, here and now, hold small promise of serving purposes other than the advancement of knowledge itself. It is the *distinctive* function of such agencies of society to take up the slack by supporting types of basic research not supported under the canons of potentials of practical relevance.

The history of science is of course replete with cases in which basic research having no immediately discernible practical implications proved eventually to have widesweeping technological consequences. The point is, however, that all apart from such windfalls, basic science lays claim to social support simply because it advances our fundamental knowledge of nature and society.

On this view, the interdependence of basic science and other social institutions is segmental rather than uniformly distributed throughout the social structure. Each class of organization, with its distinctive interests and functions, can provide support for that sector of ongoing and prospective basic research which, so far as fallible minds can judge, has the greatest potentials of relevance for it. Specialized organizations and agencies have evolved that could deliberately work to correct the major imbalances which result from the policy of potentials of relevance by supporting the basic research that would otherwise fall, largely unnoticed, into the interstices between institutionalized public and private interests.

Basic Social Research and Potentials of Relevance to Delivery of Health Care

Only now, as we near the close of this paper, do I turn to its focus: the connections between basic *social* research and the delivery of health services. The double reason for postponing this central question should be apparent to the reader who has managed to work through the preceding pages: on the view being developed here, basic social research is only a special case of basic scientific research, just as the health services organization is only a special case of organized medicine. It is being proposed that the general observations on the relations between basic science and other institutional orders of society can all be applied, with appropriate specification, to the special case of basic social research and the delivery of health services. It may be enough to trace the main outlines of the analysis, without painfully spelling out each application of the general case to the special one.

Under a policy of potentials of relevance, it is evident that in the delivery of health services, one would be primarily concerned with selected portions of basic *social* research just as, by the same logic, the telephone business is primarily concerned with basic research in physics and chemistry, the aircraft industry with basic research in aerodynamics and many related specialties, or the pharmaceutical business with basic research in chemistry and biology.

Within the broad spectrum of basic social research, however, not every part has the same potential of relevance for the distinctive problems of health services. Patterns of change in the population pyramid, in the nature of technology, and in reimbursement patterns for medical services have far-reaching effects; effects that will touch various segments of the population differently. How will people living in the new family constellations—single persons living alone or as single parents, and more likely than before to be geographically dispersed from one another—cope with problems of aging relatives who are less able to be independent? Research on the family is plainly relevant: what affects the extent to which people feel responsible for other family members not living in their households—and how does this feeling of responsibility in turn enhance or curtail their nuclear family responsibilities and their careers? We have only begun to map out and to understand current changes in the reciprocal obligations institutionalized in the American family.

In the same vein, we know next to nothing, in a systematic way, about the time perspectives of various classes of people: which of them heavily accent the future as the time of greatest significance to them, which the past, and which the short-run present? How does this differ among age strata and social classes? Is it the case that for youth, the long future looks vague and undifferentiated so that, for them, with a negligible past, only the present and immediate future are significant? How are different time perspectives linked with a concern for health—both preventative and curative measures?

Is there a wide variation in the attitudes people take toward death as an inevitability to be assiduously ignored for as long as possible or as one which, precisely because it is inevitable, needs to enter into current decisions? Only recently are medical students requesting that discussions of death, its management with patients and patients' relatives, be included in their curriculum. Under a policy of potentials of relevance, enlarged support for basic social research on this historically emerging concern is altogether appropriate. There are the dilemmas inherent in current efforts to control the costs of medical care at the same time that newly developed technologies for extending the existence of terminally ill patients involve high costs. As what point does the quality of life change the value of life? To what extent and on what grounds does a society weigh the cost of high-technology support for one type of patient over another?

Were there space to develop the point, it could be shown that the spate of basic sociological and psychological studies of the workings of small groups has direct relevance for those small groups that characteristically make up the staff on a hospital inpatient unit. These investigations are basic in that their findings are not confined, in their implications, to a narrow band of application to practice. And here, perhaps, is the place to ostracize a prevalent assumption about the distinction between basic and applied social research. It is often supposed that it is the particular groups observed in social research that determine whether the research is basic or applied. Put more concretely, this view would hold that if research on small groups happens to deal with, say, hospital patients, this at once means that the inquiry is "applied" and has significance only for this one category of group. But this, of course, is not the case. The fact that many investigations of behavior in small groups have until now been confined to readily accessible students behaving under laboratory conditions does not necessarily mean that the general results hold only for such students. Replications of some of these investigations with people drawn from industry and the military indicate that the uniformities of behavior uncovered in those studies are not peculiar to the one kind of group. The import of this is evident: if the small groups under observation were composed of physicians (rather than college students), the research would not necessarily be applied rather than basic. The difference between the two does not reside in the particular people under examination but rather in the formulation of the research questions and the design of the study, dealing, for example, with the relations among communication nets in a group, the group's state of morale, and the effectiveness of the group in task performance.

Applied social research has long been utilized by government, industry, business, voluntary associations, labor, city planning, social work, medicine and public health, and agriculture. The support of basic social research by these special sectors of American society has a relatively short history. That the conception of potentials of relevance can provide a guide to the relations between social science and health services is shown by the establishment of the Health Services Research Center as a separate government agency within the Public Health Service.

In conclusion, one can distinguish between the functions of basic and applied research and can draw upon the distinctive potentials of both. Making such a distinction can help make obsolete the old story told by Francis Bacon more than three centuries ago:

> Nor can I tax or condemn the morigeration or application of learned men to men in fortune. For the answer was good that Diogenes made to one that asked him in mockery, How it came to pass that philosophers were the followers of rich men, and not rich men of philosophers? He answered soberly, and yet sharply, Because the one sort knew what they had need of, and the other did not (2).

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What We Don't Know about Why Health Expenditures Have Soared: Interaction of Insurance and Technology

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Abstract

We review the direct dependence of medical-care expenditures on insurance arrangements and on the state of medical technology. We then direct attention to the less recognized effects of insurance and technology on each other and interactively on medical expenditures.

With so much attention to cost containment in health care, it is reasonable to assume that the causes of spiralling costs are clear. It is reasonable, but, we believe, wrong.

National health-care expenditures had reached $355 billion in 1983, 10.8% of gross national product, up from $75 billion and 7.5% of GNP in 1970, and $27 billion and 5.3% in 1960 (1). This rapid growth of expenditures on health care has prompted governmental and private purchasers of care to develop a variety of cost-containment measures. There is regulation of hospital rates based on an elaborate classification of diagnoses and procedures—the "DRGs." There are certificate-of-need programs to limit capital investment. There are professional review organizations which have the authority to disqualify patient days from payment. And there are new mechanisms, such as preferred-provider organizations, designed to bring the forces of market competition to bear more strongly on the health sector.

These efforts at cost control coexist with measures promoting quality. Occupational licensure restricts professional entry of new physicians, nurses, and other health professionals to persons who are carefully, laboriously, and expensively trained. Biomedical researchers seek ever better—but often more costly—modes of treatment, prevention, and cure. And insurance is continually being expanded to promote access to ever-higher quality—but ever more costly—care, including renal dialysis a decade ago, and liver transplants today.

There is often an implicit judgment that these health policies can be compartmentalized—one to deal with cost containment, one to maintain quality assurance, another to assure equitable access, and so forth. But matters are not so simple; goals conflict and policies interact. An understanding of these interactions is a prerequisite for sound policymaking.

To focus this paper on such interactions, we assess the state of knowledge on the growth of health-care expenditures and its two most prominently discussed "causes": the growth of insurance (public and private), and technological change. We contend that interactions between these causes are crucial.

The health-care system is a simultaneous system (Fig. 1) of insurance, technology, and health-care expenditures. This schema is obviously too simple to capture the complex effects of insurance and technology on the health-care system, but it is useful in highlighting key relationships. (Regulatory policies are set aside in the interest of simplification.)

The practical importance of the interactions between insurance and technology is great. Even large changes in the extent of insurance coverage would have relatively little effect on medical expenditures if expensive treatment technologies

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THE HEALTH CARE SYSTEM

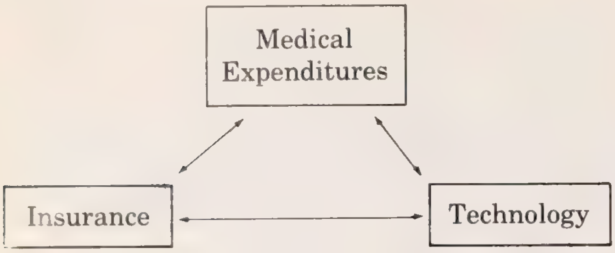

Fig. 1. The health care system as a simultaneous system; each arrowhead represents a direction of causation.

simply did not exist. Analogously, when a new technology—such as the CT scanner or organ transplantation—is developed, its speed of diffusion and subsequent effect on health-care expenditures depends heavily on the extent to which its cost can be borne through the insurance system.

(The very definition of a "treatment technology" is not entirely clear. If, for example, it were believed that blood-letting or trips to distant shrines were effective medically, then the expansion of insurance for these activities would increase their usage. To some extent, modern medicine has substituted one set of technologies for another.)

The magnitude of the effect of a *change* in either insurance coverage or technology on medical expenditures thus depends on the *level* of the other. Figure 1 also implies that a change in technology has an effect on insurance, and vice versa, leading to further feedbacks on expenditures. These interactions have barely been studied. We believe that development of expensive new procedures such as organ transplants influences the demand for public and private insurance to cover them. Conversely, increases in insurance coverage surely affect the scale and direction of medical research, ultimately influencing patterns of technological change. Though these processes and their quantitative importance are not yet well understood, they are keys to the explosion of health care expenditures.

In what follows, we first consider in more detail what is known—and what is not known—about the relationship between medical insurance and medical expenditures. We then do the same with the relationship between technology and expenditures. Throughout we highlight the ways in which interactive effects may be important.

Insurance and Expenditures

The predominant view among health economists has been that the growth of insurance is primarily responsible for the growth of health expenditures. Two prominent exponents of this view are Martin Feldstein and Mark Pauly. Feldstein wrote recently: "But the major reason, I believe, for hospital cost inflation has been the very rapid growth in insurance (2)." And Pauly began a recent paper with the statement, "The primary cause of inflation in medical care expenditures has been the extent and form of medical insurance (3)." These authors have little doubt about what is causing the "inflation" of medical care expenditures. We believe their confidence is unwarranted.

The "insurance is the culprit" view does not entirely deny the existence of advances in technological knowledge. It emphasizes that even if there had been no technological change in health care, increases in insurance coverage would have increased expenditures. We agree. There would be more amenities (color television and finer meals in hospitals), higher nurse/patient ratios, more diagnostic tests, etc., than would be the case if patients paid the full bill for each service provided. Those economists who assign primary responsibility for the growth of health care expenditures to the growth of insurance are, however, making an implicit claim that expenditures would have increased just as fast even if medical knowledge had not changed at all. Implicitly, they deny the importance of technological change (4).

Insurance as Sufficient Cause. Increases in insurance coverage do increase the demand for medical care. Perhaps the strongest evidence comes from the recent health insurance experiment financed by the federal government and conducted by the Rand Corporation. In this study, conducted in six cities, a total of 2,756 families were randomly assigned to a variety of insurance plans. The plans differed primarily in the coinsurance rate—the proportion of health care expenditures covered out-of-pocket by the patient. Because technology is presumably constant within a city while insurance coverage is allowed to vary, this experiment permits estimation of the direct effect of insurance coverage on expenditures. Preliminary results of the study clearly indicate that holding constant prior health status and other factors, reductions in cost-sharing by the family lead to higher expenditures on medical care (5, 6). Insurance increases demand by reducing the effective price of care to the consumer.

However, demonstrating that insurance affects health care expenditure is not equivalent to showing that technological change does not. Feldstein has studied insurance and hospital expenditures over time (7, 8). (As most of the literature on health expenditure growth and cost contain-

TABLE

Hospital Sources of Payment and Rate of Expenditure Increase

	Sources of payment (%)*			% Increase in expense† per pt. day	
Year	Direct	Private Insurance	Govt	Gross	Net†
1973	14.3	44.6	41.0	7.6	1.4
1974	12.9	43.0	44.1	11.2	0.2
1975	10.1	44.7	45.2	17.6	8.5
1976	10.0	45.2	44.8	14.4	8.6
1977	11.2	44.2	44.6	13.8	7.3
1978	10.3	44.4	45.3	11.9	4.2
1979	11.7	43.2	45.1	11.3	0.2
1980	12.7	41.2	46.1	13.3	−0.2
1981	12.8	40.5	46.7	16.2	5.8
1982	14.0	40.1	45.9	15.1	9.1

Sources: Authors' calculations from data contained in (1) and American Hospital Association, *Hospital Statistics, 1983 Edition.*

* Calculations exclude federal, long-term, tuberculosis, and psychiatric hospitals.

† Expenses are per adjusted patient day in nonfederal short-term general and other special hospitals, using AHA definitions. "Net" refers to the increase minus that in the all-items Consumer Price Index.

ment focuses on hospital care, our discussion does as well. Hospital care now accounts for over 43% of national expenditures on health services and supplies, up from about 34% in 1966 (1). Among the major components of health expenditures, only nursing home care has grown faster over the last twenty years.) Feldstein's findings suggest that growth of insurance is *sufficient* to explain most of the growth in expenditures. However, his estimates of the effect of insurance on health expenditures are larger than those found in most other studies that measure such effects across a sample of individuals at a point in time (as in the Rand experiment).

Unmeasured Effects of Technology. We believe that some of the effects Feldstein's model attributes to insurance are in fact the result of correlated (but unmeasured) technological change.

The U.S. experience in the past decade casts doubt on the relevance of models that focus so strongly on insurance growth. Despite a national leveling off in the fraction of hospital expenditures covered by third parties, hospital expenditures have continued to grow at very rapid rates. The Table shows recent trends in the percentage of hospital expenses covered by insurance and in hospital expense per patient day. The percentage of hospital expenses covered by insurance has declined slightly since 1976, but except for 1979 and 1980, expenses per patient day have continued to increase substantially faster than the general price level.

Proponents of the insurance explanation for rising expenditures have paid virtually no attention to the effects of technology on insurance and of insurance on technology. There is little point to insurance unless the potential costs of care are large. As technological advances have made it possible to incur staggering costs for diagnosis and cure, the demand for insurance could be expected to increase, as it did. The growth of medical insurance in this century is in part a rational response to the growing power, and cost, of medical technology.

Granting that insurance contributes to rising health expenditures, how do we decide that such increases are "excessive"? The key question is whether there are feasible ways of reducing the undesirable impact of insurance on expenditures without giving up too much of its undenied benefits in spreading the cost of expensive but effective care. If there are, why have they not already won out in the competition for the health insurance dollar?

Level vs. Growth of Insurance. What might cause the health insurance market to produce undesirable results has received little attention from economists, beyond frequent references to tax laws that encourage the purchase of health insurance by employers because it is compensation not taxable to employees. Current tax laws do lead to a higher *level* of insurance coverage than would otherwise be the case, but it is less obvious that they can account for *growth* in coverage over time. The tax law treatment of employer-paid health insurance premiums has not changed.

Effects of Insurance on Technology. In keeping with our general theme, a claim can be made that the "failure" of the health insurance market lies in an adverse effect of insurance on technology. Insurance makes important but very costly technological advances affordable, but it also enhances the profitability of expensive innovations that offer only marginal therapeutic benefits. Thus, a high level of insurance coverage can contribute to ever-growing medical expenditures. Society can pay more and more for smaller and smaller improvements in health care.

But the effects of insurance on technology are not necessarily so clear-cut. We have no reason to believe that, in the absence of insurance, the pace of technological change in medicine would have been exactly optimal. The inducement to innovation that insurance provides may on balance be a good thing. To date, theoretical (9, 10) and empirical (11) research have only scratched the surface in this very important area.

Technology and Expenditures

Since the late 1970s the subject of technology and medicine has received extensive discussion (12–18). The view that technological change is the primary cause of increasing medical expenditures has been frequently stated. Attempts to document that claim—like its counterpart focusing on insurance—have, however, not distinguished effects of technological change from those of insurance, let alone their interactions.

The simplest and most widely cited quantitative estimates of the effects of technological change on medical expenditures are studies (19–21) that involve deflating changes in hospital expenditures (per patient day or per admission) by an index of changes in input prices. Eliminating the effects caused by increased prices, the remaining effects are attributed to increased "intensity of care," or "technology."

As the authors of the original studies were aware, there are a number of problems with that interpretation. Most seriously, increases in "intensity of care" might be explained by increases in insurance coverage. These increases do not require the development of new technologies to explain them.

Equipment, Lab, and Per-Illness Costs. More disaggregated studies of increases in hospital costs are revealing, though they face the same difficulties of distinguishing effects of technology from effects of insurance, and from their interactions.

One study, of a sample of Boston hospitals from the mid-1960s through the mid-1970s, found that equipment purchases could account for only 9% of the rise in overall hospital expenses; this was contrary to the hypothesis that hospital expenses are primarily driven up by new technologies embodied in major equipment (22).

Another study indicated that increases in the number of laboratory tests, though each is relatively inexpensive, have been a significant contributor to rising hospital expenses (23).

A study of changes in the cost of treatment of selected illnesses from 1951 to 1971 (24) found substantial increases in numbers of tests even for relatively simple conditions such as appendicitis and maternity care. Another cost-of-treatment study (25) examined 11 illnesses and found that charges for 9 of them increased at least as rapidly as the hospital care component of the consumer price index. The hospital care component itself rose much faster than the general price level in the period studied, 1972–1977.

Interpreting Increases. All these studies are consistent with an emphasis on insurance as the essential explanation of rising expenditures; increases are "across the board" rather than associated with a small number of very expensive, capital-intensive technologies. On the other hand, in the Showstack study (25) the largest percentage increases in charges occurred for the two most expensive conditions, respiratory-distress syndrome and kidney transplantation. In general, between 1972 and 1977 the use of well-established procedures was relatively unchanged, but the use of new technologies such as ultrasound, nuclear medicine, and fetal monitoring increased substantially. Further, the nature of patients changed. Sicker patients could now receive kidney transplants and younger patients could now receive total hip replacements.

Taken together, these findings highlight the difficulty of separating effects of insurance from those of technological change and their interactions. Although increases in the use of new technologies are not entirely the effect of insurance, those increases are surely influenced by the extent of coverage, as is diffusion in the application of expensive procedures to broader classes of patients.

Technology and the Need for Care

Technological change can influence total medical expenditures in more subtle ways.

Technology and Increased Costs. By extending lives, technology extends the need for continuing medical care in the population. Many technologies have made it possible to keep alive individuals who would otherwise have died, and some medical costs are surely associated with the greater longevity achieved. Neonatal intensive care, for example, has been successful in increasing life expectancy of infants of very low birthweight (26, 27). While many of the additional newborn survivors will be normal, an important fraction, particularly in the groups with the lowest birthweight, will experience sustained high expenditures for medical care over their lifetimes. Victims of spinal cord injuries survive much better now than earlier in the century. They too are a group with continuing high medical expenditures (28). Gruenberg (29) argues that the conquest of infectious diseases such as pneumonia has increased life expectancies most dramatically for those persons with severe chronic conditions, who were particularly likely to die from infections in the past. He cites rising prevalences of Down's syndrome and senile brain disease as evidence. The effects of those diseases on health care costs are not in doubt.

Technology and Decreased Costs. The effects of new knowledge need not, of course, always work to increase expenditures on health care. The development of effective cures or preventive measures for nonfatal chronic conditions could lead to changes in population health that work in the direction of lowering medical expenditures. One example is the prevention of hemolytic disease in newborns through the administration of anti-Rh factor to recently delivered Rh-negative women. Not only does this prevent expenditures previously associated with the disease, it also reduces the incidence of premature births, which have their own implications for cost (30).

Need for Empirical Studies. In general, although it has frequently been claimed that the "success" of medical advances in dealing with acute illnesses has been a significant contributor to rising medical expenditures (31), this remains another area in which our empirical knowledge is still quite limited.

The High-Cost Users

Medical costs are highly concentrated among a small segment of the population, a phenomenon with important implications for understanding the growth of costs, and for cost containment policy. Zook and Moore (32) found that in a sample of six hospitals of various types, 13% of patients consumed half of all hospital resources (as measured by relative charges). Schroeder et al (33) found similar results in a sample of 17 hospitals in 1976. Only 10%–15% of all patients accounted for 40%–50% of total charges. This concentration is all the more striking when it is realized that hospital patients are themselves a small fraction of the total population. Apparently a large percentage of the high-cost users are individuals who are repeatedly hospitalized, often for the same disease (34).

Interaction with Technology. The concentration of medical costs among a small proportion of patients and its relationship to technological change deserves much more attention. Authors of the cited studies minimize the association of new technology and concentration of costs. They note that high-cost patients do not typically have a single extraordinarily expensive procedure. Rather they appear to differ from low-cost patients "more in the amount than in the kind of care they receive" (33). However, it is clear that many of these patients are kept alive, or continue to receive medical treatment, only because of recent technological developments.

These studies and others (35) have found a strong association between high medical costs and "terminal" illness. This suggests that relatively small technologically induced changes in the length of the "dying process" can have dramatic effects on total expenditures.

Interaction with Insurance. Most proposals for improving the structure of health insurance provide no incentives for reducing expenditures among the highest-cost users (36). "Catastrophic" plans—popular with academics (37, 38) and Congressional leaders (the Long–Ribicoff Bill and its successors) typically emphasize cost-sharing on small medical bills but involve some upper limit on out-of-pocket costs, beyond which expenditures are fully covered. "Procompetition" approaches such as Enthoven's Consumer Choice Health Plan (39) would similarly set up an upper limit on consumer cost-sharing.

Thus, to the extent that medical costs are concentrated among individuals whose expenditures are beyond these limits, analysts who claim that the problem is one of "overinsurance" and who have argued for some form of catastrophic insurance have presented no solution at all. Indeed, technological change may well be increasing the proportion of health expenditures that are concentrated among high-cost patients who, with catastrophic insurance coverage, would have little or no incentive to economize on even marginally useful resources.

Single "Culprits" vs. Interactive Causation

The search for a single "culprit" behind the growth of health expenditures—whether insurance or technology—is misguided; interactive effects deserve major attention. Research on the effects of health insurance on expenditures needs to be broadened to encompass its impact on the rate and direction of technological change. It is worth noting that reimbursement policies that pay a fixed rate for the treatment of a particular condition—as in the DRG system—create quite different incentives for research than do more traditional (cost-based) methods of reimbursement under insurance. In particular, the former should create some shift in emphasis from quality improvement to cost reduction. Whether such a redirection of research resources would on balance be a good thing is an open question.

Decisions about biomedical research policy must bear in mind that the use to which research findings are put is determined by incentives operating through an imperfect insurance system. We cannot assume that new techniques will be applied only in the most ideal circumstances, and this realization should influence our judgments about the potential social benefits from different lines of research.

Less is known about the causes of increased health care expenditures than is commonly believed. The general lack of success of cost-containment efforts to date reflects this. Solutions to the problems of rising health care expenditures will continue to be elusive as long as "the problem" and the causes are so poorly understood. A key, we believe, is recognition of the ways in which insurance arrangements influence the development and diffusion of new medical technologies, and of the effects of new, high-cost technologies on the evolution of the health insurance system.

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Case Studies

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Health Services Research for Hospital Policy

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Abstract

We report on a social research unit within a medical center, an arrangement which gives researchers familiarity with relevant organizational issues in a highly complex setting. Continuity in research studies permits development of historical data bases and cumulative knowledge for timely response to policy issues.

Change and continuity are polarities in a dialectical process which is the life of any organization. This process is one in which the organization interacts with its environment in a continuous exchange. A change in its environment may produce a response from the organization. That response in turn may change the environment.

To illustrate, new legislation introducing Medicaid reimbursement opened the doors of The Mount Sinai Hospital in New York City to the adjacent East Harlem community. The influx of new patients with different medical care needs led to expansion and change in ambulatory services. These changes required new positions. Minority group residents of East Harlem found new job opportunities in the hospital, increasing the economic well-being of their area. This kind of process creates a context against which the current issues of the organization must be viewed. Understanding or misunderstanding of this process, as expressed in implicit or explicit decisions, structures the direction of the organization.

Seen as an organization, a hospital has a complex environment and is itself a complex organization with many different constituencies and interests among its employees, its medical staff, and its patients. It must remain viable financially and professionally. If it is a teaching institution, it must be a viable research and teaching center. Its exchanges with its environment are numerous. It must attract patients, nurses, physicians, administrators, support staff, banks, philanthropists, students, and residents—and it must maintain all of these in a functioning state, somewhere between an optimal and a medial state of satisfaction with incentives supplied by the organization. Thus interaction with the environment is extremely complex, and at any one time the interests of all these constituencies may converge, run parallel, or clash. The function of the executives is to sort out the issues and to determine policies and priorities for the action of the organization.

It is within this context that health services research applicable to hospitals must be assessed. Often, however, health services research is not immediately relevant to policy decision-making options within a hospital.

For example, what is the relevance to a hospital of a study showing that a patient's satisfaction with health services is related to the patient's level of recovery? Or of a study (several have been done) showing that boards of directors of multihospital groups exert more managerial control over the chief executive officer than do the boards of individual hospitals?

Studies that employ variables from a scholarly discipline—sociology, psychology, or economics—often produce findings that are not specific enough for organizational decision-makers. Concepts from these disciplines can provide a way

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of looking at organizational problems and a way of thinking about them, but the variables in policy research need to be drawn from within the organization to produce change. For instance, concepts of structure, roles, and systems are useful to understanding an organizational problem. Variables of schedules, priorities, and procedures are essential to change it. A valid way of thinking in a scholarly discipline applied to variables from a given organization can result in information useful in policy making. Hospitals need studies on internal variables that they can control or on external variables to which they can adapt. What are they unaware of that they can usefully know? What are the profiles of their patients? Who are their physicians? Are their physicians' behaviors changing, and in which departments? What departments are working well, and why? Can this department which is working well be an example for other organizations? Are physician practice patterns affecting intraorganizational referrals? What is happening in different specialty practices in the region? What is happening in other hospitals?

Research Unit in Hospital. Responding to these questions and the information needs they represent, we established a health services research unit within The Mount Sinai Medical Center in New York. For such a unit to work effectively it was necessary for the researchers to determine and adapt to the aspects of the organization relevant to decision-making and to develop research approaches and methods.

Coleman (3) articulated the philosophic framework for such an approach, distinguishing sharply between a methodology that has as its base the testing and development of theories and a methodology that has as its base a guide to action. He calls research designed to advance knowledge in a scientific discipline "discipline research," and research designed as a guide to social action "policy research." The goal of policy research is not to further develop theory, but rather to provide an information base for social action, whether it is action on policy or administrative intervention.

Policy is created throughout the organization, at executive, middle management, and first-line levels; each level always retains an area of discretion. In policy research the timetable and therefore the options for design are affected by constraints and priorities. Once priorities of issues are established by the decision-makers, the objectives must translate into a research problem. After research is carried out, its results—to be useful—must translate back into terms for organizational action.

TABLE 1
Organizational Problems Classed by Visibility and Urgency of Action to Management

	Urgency	
Visibility	Urgent	Not urgent
Visible	1. Organizational Crisis	3. Recognized Organizational Stress
Not Visible	2. Anticipated Organizational Crisis	4. Unrecognized Organizational Stress

Four Types of Problems in Policy Research

In policy research, a major factor in the approach is the problem itself and its effect on the organization. We have found four types of organizational problems. These four types of problems we have named Organizational Crisis, Anticipated Organizational Crisis, Recognized Organizational Stress, and Unrecognized Organizational Stress. These four types may be understood by the relation between two organizational variables: degree of visibility of the problem to management, and urgency of action on it (Table 1).

In an *organizational crisis,* a dysfunction is widely visible to different components of the hospital. The dysfunction indicates a current or imminent disruption of the organization.

An *anticipated crisis* may arise from a diffuse problem within the organization or from an anticipated environmental change. When investigated, the problem and the extent of its risk to the organization becomes better defined.

Recognized organizational stress is acknowledged by different components of the organization as a dysfunction which reduces effectiveness or efficiency. But the organization can function or bumble on. The problem seems to require study and action, but not urgently.

In *unrecognized organizational stress,* the problem is not visible to members of the organization, but its effects can ripple through many different segments of the hospital. If it is internal to the hospital, it is frequently interpreted as the result of interpersonal problems; it may produce arguments or it may be tolerated. It is usually not perceived as resulting from the organizational structure; consequently, organizational action is not expected.

Ranking Priorities. This typology of organizational problems can be translated into a ranking which reflects administrative priorities. These priorities set the constraints on the research response. The higher the priority, the stronger the

TABLE 2

Constraints on Research Design by Administrative Priority

Administrative priorities	Research design options			
	High	Medium	Low	Minimal
High				Study of crisis
Medium			Study of anticipated crisis	
Low		Study of recognized stress		
Minimal	Study of unrecognized stress			

study constraints. Thus, high priority and research flexibility are inversely related (Table 2).

To compensate for inflexibility in research design, it is possible for a permanent research unit within a hospital to draw from acquired cumulative knowledge of the organization and a historical data base. No problem rises ahistorically, from "nowhere," without reason. Intimate knowledge of the organization throughout its political, social, professional, and fiscal structures enables the researcher to "locate" a problem quickly and to identify its components. Thus, the internal health services research office can respond to a problem which has high administrative priorities in a minimal amount of time, using necessary collaboration from a network of appropriate staff. (At Mount Sinai, the research unit is the Office of Applied Social Research, OASR, in the Department of Community Medicine.)

Case Vignettes

Organizational Crisis. In the late 1960s, consistent with the national spirit of political activism, the hospital workers' union (Local 1199) gathered strength among a poorly paid constituency. Many of its members lived in the poorer ethnic areas of New York City where federal poverty programs had brought new hope. Community residents participated in the city's community planning boards; grass-roots community organizations were established for tenants, welfare recipients, and consumers of health care, education, and other services. Among recipients of public funds, the concept of entitlement replaced the concept of charity. There was a spirit of both hope and anger. Young men who might otherwise have formed youth gangs became champions of neighborhood reform. The Puerto Rican Young Lords was an active group defending the rights of their community in an area adjacent to the hospital.

In this time of change a crisis erupted.

A rumor, which proved to be false, circulated among hospital employees that an employee had been treated with gross negligence in the Employee Health Service. The rumor heightened tension and dissatisfaction among employees throughout the hospital. The union presented a list of grievances about the Employee Health Service to the hospital administration with demands for immediate action. This demand was reinforced by rumors of a sit-in by the Young Lords, who had recently proved very effective in community actions with school and hospital administrations. All the union's demands centered around improvement of services in the Employee Health Services. The confrontation became a show of strength by the union directed at the hospital. The president of the medical center responded in two ways: by moving responsibility for the Employee Health Service from the nursing department to the outpatient department, and by ordering an immediate investigation. We, as social scientists, were asked to conduct this investigation; as members of the medical school's Department of Community Medicine but not members of the hospital, we were viewed as neutral in the struggle.

As it turned out, the precipitating rumor had no basis in reality. The ill employee had not been treated at the Employee Health Service or, indeed, anywhere in the hospital. This finding, however, was irrelevant to the crisis: once confrontational feelings erupted, they had their own momentum. Concentrating on the truth of the trigger issue might have increased the confrontation. Credibility could have become an issue between union and hospital, leading to charges of "coverup" on one side and "manipulation" on the other; to avoid either possibility, the incident was never discussed. The demands from the union with respect to the Employee Health Service became one focus of our response. The other was an assessment of the structure and function of the service itself.

Time pressure and the political climate allowed us to study the Employee Health Service with limited research objectives. Interviews were restricted to the staff of the service itself. We also reviewed correspondence, complaints, and written statements of policy and procedures.

Briefly, the study of the Employee Health Service revealed the following problems:

- discrepancies in perception and expectation of the service
- lack of integration of the Employee Health Service into the hospital operation
- absent or inappropriate lines of authority
- inadequate manpower
- overlapping and inappropriate functions for existing manpower

The study revealed a discrepancy between the hospital's, the union's, and the employees' perceptions and expectations of the service. From the hospital's point of view, the Employee Health Service was primarily an industrial health service. It provided medical-legal services to the hospital, including validation for absenteeism, compensation, and disability. Employees were permitted special benefits and courtesy services. Employees, however, expected almost complete health coverage from the service as a benefit. These expectations were reinforced by some hospital releases. The union made specific demands for changes in management and organization, based on employee expectation.

The social scientists presented these conflicting expectations as the major precipitating factor in this crisis. They recommended that the hospital clarify the role of the Employee Health Service and inform its employees and the union accordingly. (Employee expectations for delivery of medical services are common in hospitals and unique to them. Furthermore, the nature of an industrial health service presents physicians with a role dilemma: Physicians are expected to heal the sick, at the same time that they act as truant officers validating absences or sending people back to work.)

The social scientists made specific recommendations to alleviate organizational and procedural problems. The recommended changes were designed to make the service function more effectively. Most of them were implemented by the new administration. Among them was the appointment of a full-time director to the service. He reported that upon reading the recommendations, he decided to meet with all new-employee orientation groups to explain and clarify the purpose and function of the Employee Health Service. In addition, public relations descriptions and employee handbook regulations were carefully rewritten to avoid ambiguity in discussions of the Employee Health Service as an employee benefit.

The service, however, was not really integrated into the other hierarchies of the hospital. It remains a distinct support service, but for employees, not patients, and thus falls outside the main function of the hospital.

The crisis study was conducted with the understanding that a major function it served was to communicate the seriousness with which grievances were received by the president of the medical center and the seriousness of the effort to make up for the deficiencies. In response to the existence of an investigation and to a change of command, the crisis subsided. A cynic might say the gesture was enough. However, the study was conducted as earnestly but as quickly as possible, and it resulted in appropriate changes. The study required collaboration with the administration, who introduced no changes until the study was completed. They ran a holding operation by setting up a flexible mechanism for responding quickly to complaints, thus preventing a further buildup of tensions.

Anticipated Organizational Crisis. An anticipated organizational crisis may occur when a proposed or projected environmental change threatens the ability of the hospital to deliver services, or when there is a potential threat of disruption of ongoing services from within the organization. An example of a proposed environmental change and the organizational assessment of it is described by Cornbill, Foner, and Halper elsewhere in this collection of articles.

A potential threat of disruption from within the organization occurred in the emergency room of the hospital. The social scientists had worked with a group of psychiatrists to establish a psychiatric acute-care service in that area. During this period of collaborative work, the nursing and clerical staffs in the emergency room expressed concern over the lack of security from occasional violent patients, and the lack of protection for suicidal patients required to wait for the psychiatrist. Security guards had been requested to assist with these patients but had refused. Although incidents were relatively few compared to the total caseload, the potentially serious consequences warranted concern.

A conference called by the administrator disclosed that the security staff had been hired and trained only to direct traffic and to provide information, and were not to engage in any kind of police or guard work. Thus requests for such help were unexpected duties to the guards. This left a vacuum of responsibility for the security function. The consensus at the conference was that a psychiatric aide was a position necessary for the smooth functioning of the Emergency Room and for the protection of its patients and staff.

The research team was asked to justify a request to the nursing department for a psychiatric aide to be assigned to the Emergency Room with specific duties. Ordinarily, the only information available would have been complaints from the staff. Taken individually, complaints may seem idiosyncratic, and a crisis is not necessarily perceived. Because the research team had coded and analyzed material from the patient interview form, they were able to present a detailed document to the nursing service giving data to support the request. That detailed document, sent to the director of nursing, read in part:

"In the past year, the Psychiatric Acute Care Clinic located in the Emergency Room of Mount Sinai Hospital saw 1170 patients for a total of 1725 visits. . . . Both the receptionist and the Nursing Staff have to cope with situations from some of the patients for which they were not prepared to manage.

"Following is a listing of management problems that need to be the responsibility of a trained Psychiatric Aide:

"1. Patients who threaten to kill themselves are frequently unable to tolerate a waiting period and are likely to walk out before seeing the psychiatrist. Until now, the receptionist and the nurse have had primary responsibility for these patients. To illustrate the extent of the problem, among patients who were seen by the psychiatrist in 1970, 157 were evaluated as having extreme or severe suicidal thoughts and 66 patients were reported to have engaged in severe or extreme suicidal acts and/or gestures. This does not include patients reported with slight or moderate suicidal thoughts, acts and gestures. The incidence for this group is much higher.

"2. Violent patients present a problem to the staff of the Psychiatric Clinic and the Emergency Room with no one to provide back-up security. During 1970, 45 patients were evaluated as having severe and extreme homicidal thoughts, 20 had carried out assaultive acts and gestures.

"3. Frequently, patients requiring hospitalization in a municipal hospital must wait a long time for the ambulance. These patients are often anxious and agitated or are accompanied by family members who are very upset. There are often children accompanying the patient who require the support and reassurance of another adult.

"4. Families or friends who accompany patients sometimes become excited or abusive with the staff or the patients and require the presence of a person who has the time and skill to help them understand the patient, and the recommended disposition.

"5. Many patients come into the Psychiatric Acute Care Clinic in a state of severe anxiety or panic. These patients require the help of a skilled person to support and reassure them while they are waiting to see the psychiatrist.

"All of these management problems have been handled primarily by the receptionist with the back-up of Nursing Service. However, staff with the time, effort and skill necessary to adequately meet the problems described above are not available. Because these basic problems are not well managed, staff and other patients suffer from it."

The Director of Nursing answered with this memo: "Your request for a Psychiatric Aide was received on July 29th. I will discuss this request with Dr. ________ immediately and we will consider it in light of other institutional needs at this time of personnel budget planning. Thank you very much for documenting the rationale in the fashion you have. I know it will prove helpful."

The availability of specific data allowed clarification and definition of an organizational problem. To put the organizational problem into epidemiologic terms, 20 violent patients constituted a potential threat every 18 days, and 66 suicidal patients a potential threat every $5^1/_2$ days. The measurement of potential incidents legitimated the request, and a new position was submitted as a high priority on the new budget.

But organizational problems are not solved so readily. The task described did not constitute a full-time job. Additional responsibilities needed to be assessed and added to these to constitute a full-time job. Further, at the time of the budget submission, the operating budget for all services across the board was cut. One aspect of the cut was that no new budget lines could be opened. Consequently, the position remained high on the budget request until the budgetary freeze was over.

In the interim the outpatient administration, blocked from its preferred alternative, increased the number of security guards in the emergency room. Although these guards did not have a "security" function, they were viewed as policemen by patients, and it was hoped that their presence alone would act as a restraint on a potential problem patient.

In this study, very little data sufficed to document a problem and to underline the legitimacy of committing organizational resources to it. However, the data were available because of a previous research project. Response to a documented problem by an organization is often slow because there are procedures to be followed and other alternatives to be weighed. When a change is then introduced, it takes more time and elaboration to integrate it into the existing structure.

Recognized Organizational Stress. Upset about the long waiting time in the Emergency Room, the Ambulatory Care Committee of the Medical Board requested the social scientists to do a study of patient flow in the Emergency Room. The problems were formulated and a system of data collection was designed by the OASR. The entire staff of the Emergency Room collaborated in data collection. With the collaboration of the Emergency Room staff, the study was to address questions at the level of the Ambulatory Care Committee of the Medical Board, the middle management medical, nursing, and administrative staff responsible for the Emergency Room, and the subordinate first-line staff responsible for direct patient care in the Emergency Room.

The purpose of the study was to establish actual waiting times in the Emergency Room and to identify the nature and reasons for excessive waiting so that remedial action could be initiated.

The report produced by the social scientists was based on data from the 1,000 patients treated during one week in the Emergency Room. It focused on the waiting times of patients in the Emergency Room prior to screening by the nurse. It became apparent that patients waited too long before they were screened by the nurse, and moreover that no uniform guidelines were followed in establishing patients' acuity of condition.

This led to the development of a new screening instrument by the nursing staff, collaborating with physicians. Using this instrument, patients arriving in the Emergency Room were screened by a nurse trained in ranking the acuity of care required before the patient registered with the clerk. As a result, waiting time between patient arrival and screening were considerably shortened, and patients with higher acuity received uniformly appropriate priority treatment.

The findings in this study thus revealed one problem with potential crisis implications. The hospital could have been in legal difficulties if anything had happened to a patient waiting excessively long to be screened by a nurse. Once the risk to the hospital was made visible, the administration moved immediately to design a new screening system and to train the nursing staff in its use.

The other findings had to do with problems of recognized organizational stress, which were further studied, adding to organizational knowledge; none, however, required urgent action.

The second step in the study analyzed the effects of X-rays, laboratory tests, and consultations on the time patients spent during the day, evening, and night shifts in the Emergency Room. With minor variations, the number of X-rays, laboratory tests, and consultations was proportional to the volume of patients in each shift. For instance, 56% of the visits occurred during the day shift, and 56% of the X-rays were requested during the day shift. This correspondence pointed toward a possible basis for predicting demand for Emergency Room services but to validate it, other times of the year had to be sampled. Furthermore, there might be variation in the amount of ancillary services ordered, depending on the experience level of the examining physician. New residents in the Emergency Room tend to order more tests than those with more experience.

To assess the relative effect of ancillary and consulting services on total time spent in the Emergency Room, patients were classified by requests or lack of them for X-rays, laboratory tests, and consulting physician services in any possible combination. It was thus possible to place each patient in an exclusive category and, using median waiting times, perform a systematic comparison and ranking of differences in waiting time. This enabled the study to show the effects of each ancillary service and physician consultation on the total waiting time for Emergency Room patients in each shift.

The median waiting time, without any additional service request, was relatively constant for all 3 shifts. However, during the day shift X-rays took relatively longer, and during the evening shift, laboratory tests took longer. During the day, X-ray personnel had to accommodate patients from the clinics as well as the Emergency Room.

This study answered specific requirements of the administrative and executive staff with respect to the issue of time required for the different services in the Emergency Room (Fig.). It did not give all the answers needed for a decision, but led to a series of studies of problems that had become visible. The time required for laboratory tests at night, for instance, resulted in a study of the microscopy services that showed that routine tests from the inpatient surgical floors arrived in batches right after midnight, suddenly increasing

Median Patient Waiting Time in the Emergency Room, The Mount Sinai Hospital, by Service Requested, 1980

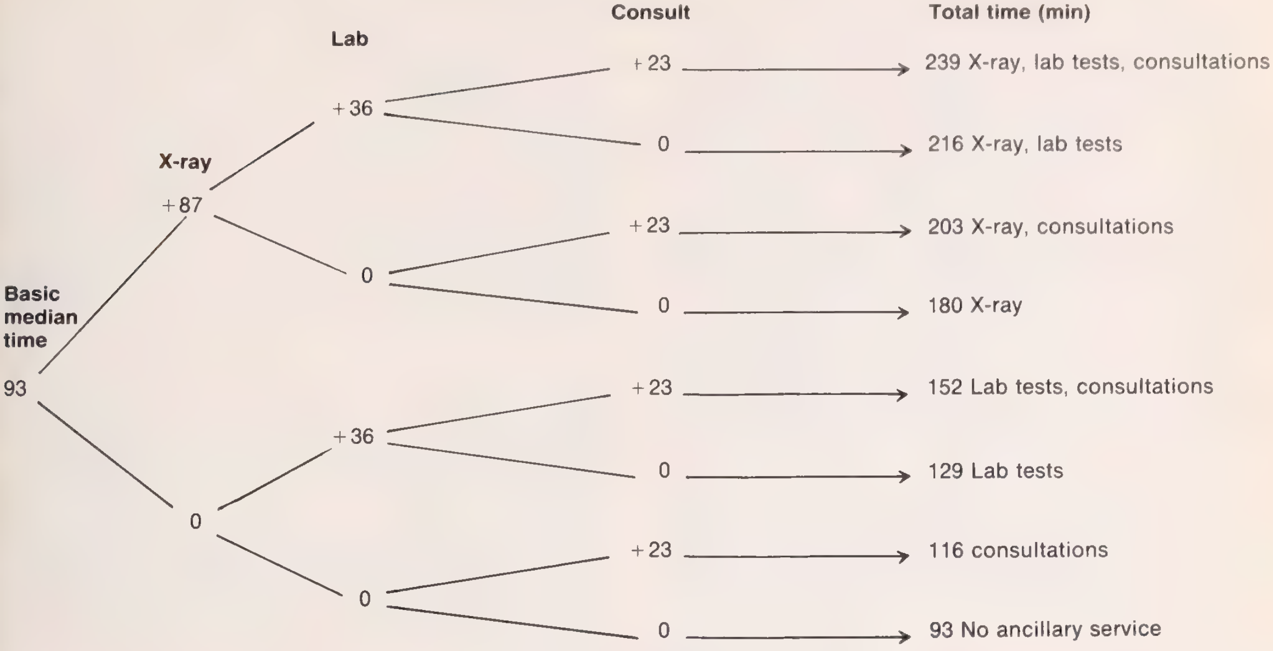

Fig. Decision tree.

the workload. Review of the problem led to a change in procedures that shortened laboratory response times at night.

Unrecognized Organizational Stress. Unrecognized organizational stress is invisible to operational or executive staff until it is uncovered in the course of collecting and ordering data from and about the hospital. One such identification of a problem in the course of exploratory research came from data the OASR pulled out of the inpatient files.

We knew Mount Sinai was a nonsectarian hospital serving an extensive community. However, it was founded as a Jewish hospital and keeps its special ties to the Jewish community. Since World War II, a great deal has changed in American society in general and for Jewish physicians in particular. Quotas in medical schools and restrictions on residencies and appointments in hospitals for Jewish physicians no longer exist. What implications might this have for the identity of the hospital as one particularly related to the Jewish community? What implications might this have for the identity of Mount Sinai as a Jewish hospital, and for Jewish philanthropy?

We compared the inpatient population for four successive years (1976–1979) to discover that the proportion of Jewish inpatients declined slightly but significantly. There was little change in actual numbers but an increase in the number of admissions of non-Jewish patients. Most of the increase was among patients living in poor areas and reimbursed by Medicaid, in contrast to most of the Jewish patients, who lived in middle-class and upper-class areas and were largely reimbursed by Blue Cross.

We looked at the age pyramids of inpatients by religious preference and found that the Jewish population within the hospital was much older than non-Jews. The phenomenon we reported to the administration was the aging of the Jewish population the hospital was serving. In the future, if trends continued, the hospital might be serving fewer Jews and changing its special relation to the Jewish community.

There were many plausible reasons for the aging of the Jewish community. Following World War II, major demographic changes took place nationally, young families moving from urban to suburban areas. Nationally the Jewish population was an aging one with a low birth rate, low in particular compared with many of the new immigrant groups coming into New York City. This information raised questions but could not propose answers.

However, a year or so later, a survey was being conducted by another agency to update Jewish demography in Manhattan, and the hospital joined it and added a couple of questions about places of hospitalization. The results allowed us to enlarge our information base. We found that other hospitals were indeed competitive among younger Jews. However, from an earlier study we knew that the majority of patients for any hospital, medical center or community hospital, lived primarily in the area surrounding the hospital. The data confirmed that Jewish patients were following this tendency, which is not difficult to understand. Physicians like their offices reasonably close to the hospitals with which they are affiliated. Most patients go to physicians in their residential area. Once patients have chosen a primary physician, they usually stay in that physician's referral system, which is generally among colleagues affiliated at the same hospitals.

Thus, demographic changes could account for changes in the larger number of admissions of younger Jewish patients to other hospitals. This is confirmed by looking at the relation between age, income, and residence.

We confirmed from the data that older age, up to retirement, is correlated with higher income and is concentrated in particular residential areas according to income. Consequently, hospitals located near older-age, higher-income residential areas draw more of such patients; hospitals in areas populated by younger families and children draw from those groups.

Although local hospitals are generally preferred, there are exceptions. From other, previous studies, we could show that specialty services draw from a much wider geographic area than do more general or primary services. One effect of excellent specialty service is the ability to attract patients from a more extensive residential area. Enhancing facilities for certain specialties might be a means of changing existing patterns of referral.

Discussion

Communicating Results. Time and careful thought must go into the presentation of information in the report of each study. Among executives and operating staff, a series of often discrete actions is the pattern of the day. A voluminous report can represent an obstacle. It may not be read, or it many not be read carefully. For instance, the use of a decision tree (Fig.) to illustrate the major findings in the study of patients' waiting time in the Emergency Room enabled the reader to see the results of the study on a single page.

Information is also valuable only if it is succinct and clear in its implications for the issue under discussion and the "nest" of its context—all the other factors affected when a change is made or a new feature introduced into an organization. The context is in the consciousness of the operational staff. The research report must help the staff make connections.

Context as Vital. In the studies described here, it was important for the research staff to understand the context of the organization. This kind of knowledge comes only with some years of experience working in different settings within the hospital; the researcher learns about it from the point of view of the operational and executive staff who are responsible for it. However, even such exposure is not enough. The organization constantly changes, and a flow of information about such changes from various sources is vital.

Also crucial is protection of the staff with whom the researchers work. The professional, operational, and administrative staff of the hospital are essentially the researchers' colleagues and collaborators. Their personal and professional integrity must be protected at every level. For instance, a problem uncovered with a clerk is first reviewed with the clerk, not with the supervisor. Both clerk and researcher address the problem in the clerk's jurisdiction, referring to the supervisor what is not in the clerk's jurisdiction, until all the issues are presented in a shared report.

In-Hospital Research Unit. The need for policy research at the national level is clear. We believe policy research is equally useful at the level of the individual organization—but the subjects of investigations vary.

Nationally, for instance, the new reimbursement system has successfully reduced hospital costs paid by the government and insurance carriers. However, by reducing the census of individual hospitals, it has raised the cost of delivery of services to individual patients. The large overhead of hospitals has to be allocated among fewer patients. If charges are controlled but costs increase, hospitals need to develop new strategies for survival. This is an area in which the internal research unit can be useful to the hospital.

What is absolutely paramount is collaboration and mutual trust between the research office and the operational staff of the hospital. In our own work, the Director of Planning and Management Information Systems encouraged and supported our efforts. His decision to make the data processing files accessible, after permission had been granted by each department, enabled us to broaden the scope of our efforts. We were able to accumulate annually and to integrate a data base from the files of different departments, thus giving us current and historical data bases. Furthermore, we were able to establish the patient as the unit of the data base, rather than the visit or the discharge.

Ongoing relations with many hospital staff members are an essential part of our ability to work within the organization; from these experiences we have derived many of the principles and ways of working of the research unit. Over the course of the years, we have studied and participated in changes in inpatient services, the Emergency Room, Unit Management for Nursing Stations, pediatric services, various clinics, and an experimental Child Health Station, as well as broader hospital policies. Support and encouragement from our users has been essential; part of our basic task has been to keep that a two-way street.

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Health Services Research in Action: Explaining a Decrease in Patient Visits at a Diabetes Clinic

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Abstract

This paper describes an application of health services research in action at a medical center. The process involved the analysis of an operational problem, the declining population in a clinic, using a historical data base established by a group of social scientists in an in-house research office. Findings from an examination of visit trends and patient characteristics were presented by the social scientist and discussed in meetings with the director of ambulatory care and the chief of the clinic concerned in a collaborative problem-solving effort. To interpret the data, an understanding of the context inside and outside the hospital was essential.

Concerned with day-to-day operational issues, managers are trained to make short-term comparisons of organizational performance. To help evaluate longer-term changes in organizational performance, in the mid 1970s the Office of Applied Social Research (OASR) developed clinic profiles (1) as a management device. These clinic profiles show actual quarterly visits over a period of 7 years with a moving average trend. The moving average trend is designed to eliminate quarterly variations and to highlight the direction in which visit volume is moving. These clinic profiles, produced once a year, are used by the administration to monitor visits in the 154 clinics of the out-patient department. If changes in clinic performance warrant, the manager also uses the profiles in reviewing clinic operations with clinic chiefs.

Reviewing the clinic profile for 1984, the ambulatory care administrator observed that the Diabetes Clinic at The Mount Sinai Hospital had experienced a decline in visits which was more extensive than that of other clinics. Once alerted, he requested the OASR to examine the reasons that might have contributed to the decline in visits.

The social scientist produced a report (2) based on an analysis of the characteristics of Diabetes Clinic patients and visit patterns from 1978 to 1984. Data for the study were based on statistical reports on ambulatory care and tapes containing data for 100% of the patient population and its use of hospital services at The Mount Sinai Hospital. We describe the report and the findings presented in it in order to illustrate how research can be made useful to operational staff. The report led to further collaboration through the social scientist's subsequent discussions with the administrator and the chief of the Diabetes Clinic, in which the appropriate administrative response to the data was determined.

The Data

Visit Patterns at the Diabetes Clinic. Visits to the Diabetes Clinic showed a progressively declining trend since 1980 (Fig.). By 1983, the actual number of visits had dropped 17% below the

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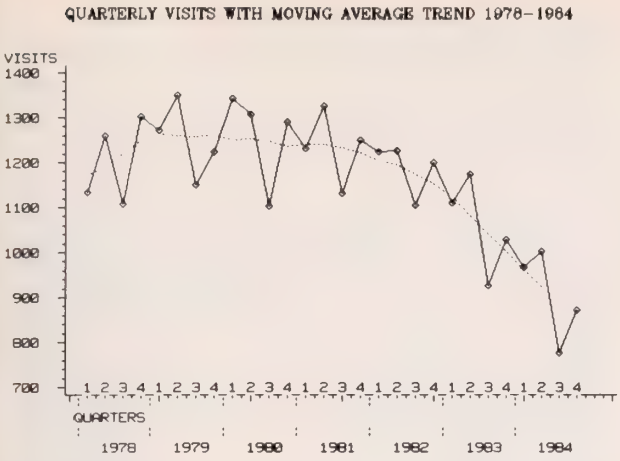

Fig. Quarterly visits to Diabetes Clinic, The Mount Sinai Hospital, with moving average trend 1978–1984. Visits for the third quarter, 1984, have been estimated to compensate for a 47-day long strike, to maintain a comparative historical data base.

1980 level. There was no obvious explanation for this decline, which was much longer and sharper than any other clinics had experienced.

To assess whether decreases in number of visits reflected a change in visit pattern or in patient volume, the social scientist first examined the number of patients seen annually and the visit rate in the Diabetes Clinic from 1979 to 1983 (Table 1). The number of patients dipped in 1980, then partially recovered in 1981, but declined thereafter at approximately the same (accelerating) rate as the visit rate. The average number of visits per year remained remarkably steady throughout the five-year period, except for 1980. The decrease in visits clearly resulted from a shrinking patient population in the clinic, and not from a change in treatment pattern.

Sociodemographic Characteristics of Clinic Population. From 1982 to 1983, the number of patients using the Diabetes Clinic decreased 10%. Data were analyzed to determine if certain groups of patients were more affected than others. If the 10% decrease occurred in patients living in a particular area, or of a particular age or income grouping, the percentage of that group in the clinical population would decrease steeply. If, on the other hand, all groups decreased equally, there would be no difference in proportions from one year to the next (Table 2).

TABLE 1

*Diabetes Clinic: Patients and Visit Rates, 1979–1983**

Year	No. of Pts	Annual change %	Visit rate
1979	1,237	—	4.0
1980	1,203	−3%	4.2
1981	1,221	+1	4.0
1982	1,182	−3	4.0
1983	1,066	−10	4.0

* Data for 1984 were excluded because the clinic was closed during a 47-day hospital workers' strike.

Scarcely any such sociodemographic change occurred in the Diabetes Clinic population from 1982 to 1983. Except for patients from the Bronx, who decreased 2%, no group increased or decreased by more than one percentage point. The Diabetes Clinic must have lost more patients by attrition, recruited fewer patients, or experienced a combination of these two factors to account for the change.

Changes in Number of New Patients. In 1980, the first year data were available on 100% of the Diabetes Clinic population, all patients were new by definition (Table 3). In 1981, 340 patients, or 28% of the Diabetes Clinic population, had not been seen in 1980 and were therefore new. In

TABLE 2

Diabetes Clinic: Distribution of Patients by Residence, Age, and Pay Status, 1982 and 1983

Sociodemographic characteristics	1982 (N = 1,182) %	1983 (N = 1,066) %
Residence		
East Harlem	35	36
Bronx	26	24
Other Manhattan	25	25
Queens	8	7
Brooklyn & Staten Island	4	4
Not NYC	2	2
Age		
to 20	*	*
20–24	2	2
25–29	4	4
30–34	5	4
35–39	5	4
40–44	6	6
45–49	9	9
50–54	11	12
55–59	13	14
60–64	13	13
65–69	12	11
70–74	9	10
75–79	6	6
80–84	3	4
85+	2	2
Pay Status		
Medicaid	30	30
Selfpay	27	28
Medicaid/care	20	20
Medicare	19	18
Employee	4	4
	100%	100%

* Less than 0.5%.

TABLE 3

"New" Patients Treated in the Diabetes Clinic, 1980–1983

Year	Total Patients	New Pts as % of total
1980	1,203	—
1981	1,221	28%
1982	1,182	25%
1983	1,066	22%

1982, 25% were unknown from previous years; in 1983, 22%. Although the short period available to analyze changes in new patients entering the Diabetes Clinic limits our interpretation, it is obvious that part of the decrease in Diabetes Clinic patients results from the steady annual decline in the number of new patients. But this alone did not account for all the decline in the volume of Diabetes Clinic patients.

Changes in Dropout Rate. To study the dropout rate among clinic patients, we selected all patients who had attended the Diabetes Clinic in 1980 and followed them over a period of four years. Of the 1,203 patients seen in 1980, only half were still using the Diabetes Clinic in 1983. The largest drop occurred in 1981, when 27% of the original group dropped out. Subsequently, patients left at a lower but similar rate: 16% in 1982 and 17% in 1983. Obviously, the dropout rate of the diabetes patients did not accelerate over time.

Identifying Types of Users: "Core," "Lapsed," and "Transient." To understand the process which kept some patients in the Diabetes Clinic and lost others at different intervals, we examined use patterns. Three types of Diabetes Clinic users emerged, which we classified as core, lapsed, and transient. The core patients were those who remained with the Diabetes Clinic throughout the four years; lapsed patients were those who stayed for 2 to 3 consecutive years; transient patients were those who attended the clinic during one or two nonsuccessive years.

Core patients were active in the Diabetes Clinic throughout the four years; all of them were also visiting other outpatient areas during this time (Table 4). In the third year, half of the lapsed patients dropped out of the Diabetes Clinic and about a third left the hospital altogether. In 1983, the fourth year, none of the lapsed patients were visiting the Diabetes Clinic anymore, but a quarter of them were still using other outpatient services. Transient patients dropped to a trickle in the Diabetes Clinic after one year; however, between 30% and 40% of them continued to be relatively stable users of other hospital outpatient services during the three subsequent years.

The relatively brief Diabetic Clinic encounters of the transient patients suggest patients newly entering the system who were being tested for symptoms of diabetes. The longer involvement with the Diabetic Clinic by the core and lapsed patients points towards a population of long-term diabetics.

Use Characteristics of Each Type. Interestingly enough, all three user groups had extremely high visits. In 1980, core patients averaged 11.6 visits, lapsed patients averaged 10.7 visits, and transient patients averaged 9.7 visits (Table 5). Core and lapsed patients used similar clinics at similar rates in 1980, whereas transient patients were distinctly different.

Core and lapsed patients were intensive users of the Diabetes Clinic, averaging 5.1 and 4.4 visits to it. Transient patients visited it less frequently, averaging 2.3 visits per patient. Their highest visit rates occurred in the General Medical Clinic, the newly established Internal Medicine Associates group practice (IMA) and the nonmedical clinics. All three groups used the Emergency Room (ER) and the medical specialty clinics at similar rates in 1980.

Core patients maintained a relatively stable visit rate in all outpatient services over the four-year period. They are obviously long-term diabetics with well-established treatment patterns.

Lapsed patients were the only group whose total hospital visit rate increased during the four years. It rose to a high of 16.0 visits in 1981, then levelled off to 13.3 visits in 1983, still three visits above the rate of the core patient group. The increase in visits occurred only in visits to the IMA

TABLE 4

Use of Diabetes Clinic and Other Outpatient Services in 1980–1983 by 1980 Diabetes Clinic Patients

	Diabetes Clinic		Other outpt. services	
Type of Patient	Pts. (%)	Visit rate	Pts. (%)	Visit rate
Core				
1980	590 (100)	5.1	590 (100)	6.5
1981	590 (100)	5.1	590 (100)	6.3
1982	590 (100)	4.9	590 (100)	6.0
1983	590 (100)	4.7	590 (100)	6.0
Lapsed				
1980	281 (100)	4.4	281 (100)	6.3
1981	281 (100)	3.5	281 (100)	12.5
1982	129 (46)	3.1	178 (63)	10.5
1983	— —	—	73 (26)	13.3
Transient				
1980	332 (100)	2.3	332 (100)	7.4
1981	10 (3)	3.4	142 (43)	5.5
1982	26 (8)	2.7	116 (35)	7.5
1983	27 (8)	2.7	105 (32)	6.1

TABLE 5

Use Patterns of 1980 Diabetes Clinic Patients: 1980–1983

	Core Patients				Lapsed Patients				Transients			
	80	81	82	83	80	81	82	83	80	81	82	83
Outpatient Area Used												
Diabetes Clinic	590	590	590	590	281	281	129	—	332	10	26	27
Emergency Room	280	275	273	259	135	120	100	44	162	79	70	58
General Medical Clinic	56	28	24	12	32	17	24	14	74	45	26	14
Internal Medicine Associates*	3	8	9	23	—	8	15	25	2	13	18	31
Other medical clinic†	210	171	165	187	97	67	42	16	128	36	27	30
Other clinic	370	351	348	331	176	158	99	42	184	93	77	65
Total	590	590	590	590	281	281	178	73	332	142	116	105
Visit Rate												
Diabetes Clinic	5.1	5.1	4.9	4.7	4.4	3.5	3.1	—	2.3	3.4	2.7	2.7
Emergency Room	2.4	2.6	2.2	2.5	2.3	2.3	2.2	2.3	2.6	2.7	2.6	2.3
General Medical Clinic	2.4	2.3	2.2	1.2	3.0	3.4	2.6	2.7	3.9	4.5	3.9	2.9
Internal Medicine Associates*	2.3	5.8	2.6	2.5	—	3.8	3.1	5.3	4.5	4.0	5.2	3.8
Other medical clinic†	3.9	4.1	4.1	4.4	3.3	4.0	5.4	8.1	3.3	6.0	6.8	5.7
Other clinic	5.9	6.2	6.1	6.2	5.9	5.7	3.9	3.8	7.2	5.9	7.1	6.0
Total	11.6	11.4	10.9	10.7	10.7	16.0	13.6	13.3	9.7	8.9	10.2	8.8

* Group practice established in 1979 to replace the General Medical Clinic.

† Excluding Neurology and Neoplastics services.

and other medical specialties. Visits to the Diabetes Clinic decreased and finally disappeared in the fourth year. Considering their previous intensive and consistent use of the Diabetes Clinic, it seems unlikely that these diabetics ceased to require treatment for their condition. It is more reasonable to assume that they switched their source of care.

Among the 25% of lapsed patients who remained within the hospital system, a third were using the IMA by 1983, accounting for an average of 5.3 visits, or almost a quarter of all their visits. In 1980, none of them used the IMA, which had only begun operations the year before. Transfer of the lapsed patients to the IMA was accompanied by a reduction in the average number of visits to the nonmedical clinics but an increase in the use of the medical specialties, reflecting the IMA approach of appropriate and comprehensive referrals to specialty clinics. The 74% of lapsed patients who left Mount Sinai altogether must have moved to another source of care, possibly another hospital or a private physician.

Judging by the length of time lapsed patients had been visiting the Diabetes Clinic, they were definitely long-term diabetics who either substituted care in the IMA for care in the Diabetic Clinic, or left the hospital to be treated elsewhere. They might never have required the specialty care of the Diabetes Clinic if a clinic such as the IMA had existed at the time they entered the outpatient department. This supposition has been corroborated by informal communication from an IMA physician.

If visit rates are an indicator of severity of illness, transient patients were less severely ill than either core or lapsed patients. The majority of the transient patients may not even have been diabetics. A few who were diabetics remained to be treated either in the Diabetes Clinic or in the IMA. All transients who stayed with Mount Sinai through 1983 were heavy users of other medical specialty clinics and nonmedical clinics.

Sociodemographic Characteristics of User Types. The three user groups differed somewhat in their sociodemographic characteristics. Transient patients tended to be younger than either core or lapsed patients: 41% of the transients were under 50, compared to 19% of the core and 20% of the lapsed patients.

The largest proportion of the core patients (40%) lived in East Harlem, which is adjacent to the Medical Center, whereas the largest proportion of the lapsed (30%) and transient (30%) patients lived in the Bronx, which is north of and somewhat further away than East Harlem.

Transient patients had the largest proportion of selfpay (36%) and Medicaid (29%) financial status. Because core and lapsed patients were older, a larger proportion were Medicare-paid or Medicare-plus-Medicaid paid.

In 1983, 50% of the original panel of 1980 Diabetes Clinic patients continued visiting the Diabetes Clinic, 13% were still using other outpatient clinics and 35% had dropped out of Mount Sinai Hospital altogether.

Those patients who continued visiting the Diabetes Clinic were predominantly core patients

TABLE 6

Sociodemographic Characteristics of 1980 Diabetes Clinic Patients by Use of Diabetes Clinic and Other Outpatient Services in 1983

	Total (n = 1186) %	Yes Diabetes Clinic (n = 612) %	No Diabetes, Yes Other (n = 151) %	No Diabetes, No Other (n = 418) %
Age				
Under 50	25	19	35	31
50 & over	75	81	65	69
Residence				
East Harlem	36	40	40	29
Other Manhattan	23	25	19	23
Bronx	26	23	28	30
Queens	8	7	10	10
Bklyn	4	4	1	5
Not NYC	2	2	3	2
Pay Status				
Medicaid	26	25	36	23
Medicare	21	22	17	21
Medicaid/care	23	25	23	18
Selfpay	28	24	23	34
Employee	3	3	2	2
Total	100%	100%	100%	100%

50 years of age or older who lived in East Harlem. (Table 6) Those patients who stopped visiting the Diabetes Clinic were mostly transients and lapsed patients under 50 years old. If these patients remained active in other clinical areas, they tended to have Medicaid coverage and live in East Harlem. These were most likely patients who no longer required the specialty services of the Diabetes Clinic after they began receiving primary care from the IMA.

Patients who left Mount Sinai altogether were more likely to be selfpay patients who lived outside East Harlem. However, they also included a larger proportion of patients over 50 who lived in the Bronx, Queens, and other areas of Manhattan who were covered by Medicare. Because of the large number of lapsed patients with these characteristics whose intensive use of the Diabetes Clinic in prior years indicates they were long-term diabetics, we assume that these patients chose another source of care outside The Mount Sinai Hospital.

Discussion

"An organization is a living system. . . . It grows and develops, has a history, experiences crises and adapts" (3). The medical center is such an organism. Its organization is comprised of interrelated subsystems which pursue its common goals of teaching, research, and services through an extensive division of labor and technology. Functioning under the constraints of both a competitive and also a highly regulated, rapidly changing health care system, the medical center must constantly relate and adapt (4). As a result, the challenges and tasks of governance and management have become increasingly complex, requiring a greater need for organizational knowledge by the system's managers for planning and control decisions (5).

The Office of Applied Social Research (OASR), a part of the Department of Community Medicine, has played an active role in the shaping of this knowledge, providing health services research in collaboration with the medical center, in a form that is relevant and appliable by management and planning staff (6).

Applied health services research cannot be effective unless the findings produced by the social scientists are directed to and understood by the users, in this case the ambulatory administration and the chief of the Diabetes Clinic. Drucker has pointed out that the user is "the channel through which the [social scientist] directs his knowledge, his work and his capacities toward joint results, and through which in turn he finds out the needs, the capacities, and the opportunities of the organization" (7).

The findings reported by the OASR led to several meetings of the director of ambulatory care, the chief of the Diabetes Clinic, and the social scientist. Discussions centered on the interpretation of the findings and possible need for organizational action. Through the discussions, a composite of factors emerged to explain the decrease in use of the Diabetes Clinic. Some of these factors were external, others were internal to the organizational environment.

External Factors. The chief of the Diabetes Clinic helped place the decline of the patient population in the context of larger environmental changes. The Diabetes Clinic is one of the oldest specialty clinics at The Mount Sinai Medical Center. Opened in 1917, the clinic remained a leading center for diabetics in New York City until the advent of Medicare and Medicaid, which made specializing in the care of diabetes more economically feasible for other providers of care. There are now more private practices and clinics available for the care of diabetics in many areas of the city than ever before. Consequently, Mount Sinai's Diabetes Clinic has more outside competition than ever. Patients who used to travel long distances to visit Mount Sinai's clinic can now receive treatment nearer their homes. This is corroborated by our finding that the lapsed patients, those who once used the Diabetes Clinic intensively for long periods and now have stopped visiting The Mount Sinai Hospital altogether, lived predominately outside the immediate neighborhood of the hospital. For older patients who were on Medicare, convenience of location may have determined a switch to another provider. Selfpay patients who left may have been motivated by financial considerations as well as location. Increases in clinic fees and pharmacy prices, as well as the introduction of a charge for prescriptions, could have deterred patients who found comparable services at similar prices closer to their homes.

Internal Factors. Changes also occurred within the organizational environment of the hospital which affected the activities of the Diabetes Clinic. Two new centers for primary care introduced a conscientious effort to restrict Diabetes Clinic attendance to patients whose major problem is diabetes.

The first primary care center was the Internal Medicine Associates (IMA), a group practice phased in over a period of four years to replace the traditionally run General Medical Clinic. Patients with less severe diabetes who would previously have been referred to the Diabetes Clinic were now treated in IMA. The second primary care center, the newly established Geriatrics Clinic, was also absorbing—but to a lesser extent—patients from the Diabetes Clinic who could be more appropriately cared for in the geriatrics setting. These two new clinics helped reduce the number of new referrals into the Diabetes Clinic and at the same time absorbed Diabetes Clinic patients whose diabetes was not severe.

This development coincided with a change in physician staffing. The retirement of several clinic physicians, and reduced coverage by voluntary physicians from two sessions to one session per week, decreased physician hours in the clinic. These developments resulted in longer queues and also contributed to the loss of patients already established in the clinic who could now find services closer to home. To alleviate the decrease in physician hours and at the same time make more efficient use of provider time, a Diabetes Management Clinic was opened early in 1984. That clinic, staffed five days a week by a nurse clinician, sees new patients waiting for appointments to the Diabetes Clinic. It also assists the Diabetes Clinic in monitoring patients whose diets have been changed or whose medication has been adjusted in the Diabetes Clinic.

Figures combining visits to the Diabetes Management Clinic and visits to the Diabetes Clinic show a levelling off of the downward trend. Together, these two clinics, which are for the more severely ill diabetic patients, have been maintaining a lower but constant level of visits since the middle of 1984. The loss in number of patients and per-patient visits which occurred during the preceding years was the result of shifts in the external and the internal organizational environments. It was a natural, adaptive response to internal and external changes. In addition to this natural response of persons seeking health care, the hospital also responded to change by planning and establishing the Diabetes Management Clinic, which succeeded in stabilizing patient and visit volume. No further questions or actions were necessary.

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Evaluating a Proposed Change in a Delivery System and Reimbursement Structure: A Case Study of Planning for a Hospital

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Abstract

We present a case study illustrating the analysis and evaluation of a proposed alternative method of providing care for a select group of patients in a major medical center. The paper examines the medical center's response to a proposal developed by the city government to institute a capitation program for one group of Medicaid recipients and providers. The study highlights the need for data specific to the individual institution in analyses of health services. The focus is on those operational and financial issues that would have been generated by a new program and reimbursement structure.

Background. In recent years state and local government have begun to explore alternative methods to control Medicaid costs (1, 2), most notably in several capitation demonstration projects targeted for Medicaid enrollees. One such project was proposed in New York City. In October 1983, the NYC Health and Hospitals Corporation, in conjunction with the Human Resources Administration, drew up a proposal—the Primary Provider Demonstration Project (PPDP)—to change the delivery and Medicaid reimbursement system for patients living in an area adjacent to The Mount Sinai Hospital and submitted it to the President of The Mount Sinai Medical Center. Its stated purpose was to save Medicaid program expenditures and at the same time to improve quality of patient care. It mandated a prepaid capitation program for all Medicaid enrollees in the targeted area, and prescribed a case management approach with an emphasis on preventive services. The population to be served would be Medicaid recipients in one zip code area of Manhattan, adjacent to the medical center.

At the request of the senior management of the hospital, a task force, with representatives from several clinical and administrative areas, was formed to analyze and assess the impact of this proposal on the hospital.

Project Description. The proposal required Medicaid enrollees living in the target area to choose one provider among several qualified providers and stay with that provider for one year after an initial 30-day trial period. Medicaid eligibility for enrollees would be extended from one month to six. As could be expected, the compulsory sign-up feature met with considerable community resistance (3). The providers could be hospitals, neighborhood health centers, or private physicians in contiguous zip codes adjacent to the target area.

A central feature of the proposal was that one physician, the case manager, would be responsible for the management of each patient to assure continuity of care and minimal duplication of services. The major responsibility of the case managers would be the coordination of all health care services for enrollees, either directly or through a subcontractual arrangement. This would encompass provision of primary health care (including 24 emergency services), specialty referrals, and ancillary services. Each provider would have to assign specific board-certified primary care physicians as case managers.

Providers would be reimbursed on a capitation

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basis. They would receive fixed monthly payments for providing *all* covered services. The proposed capitation rate included payment for all Medicaid-covered services except institutional long-term care, home attendant and housekeeping services, Methadone Maintenance Treatment programs, and psychiatric care greater than 30 days.

The program would be administered by a local office of the New York City Human Resources Administration. This office would act as the middleman, to clarify beneficiary and provider relations, assure quality, and provide management information system support. An Advisory Council consisting of providers, Medicaid enrollees in the designated area, and public officials would be established.

Structure of the Analysis. Since the PPDP would have different effects within the medical center, it was felt that the analysis should encompass two components: a centerwide perspective, and a more specific departmental perspective. Clearly, certain aspects of the progam that might be beneficial to the center as a whole might be detrimental to particular departments. This aspect required closer scrutiny. Additionally, it was considered appropriate to assess both the medical center's participation and nonparticipation in the program.

Given the range of the analysis, a centerwide task force was chosen as the most appropriate mechanism to examine the impacts of the program. At the medical center, the departments of Pediatrics, Obstetrics, and Medicine were considered the most appropriate to provide case managers. Consequently, representatives from these clinical areas were included in the task force. Also represented were the departments of Finance, Ambulatory Care Administration, Community Medicine, and Planning and Management Information Systems. Thus, the task force membership combined the necessary expertise in clinical, operational, and research areas to analyze the effects of Mount Sinai's participation or nonparticipation in this program.

The task force decided to examine the potential impacts of participation and nonparticipation in three areas: patient utilization, organization, and finance. Specifically, critical reviews of the programmatic and administrative aspects of the proposal were prepared by the departments; and a financial model was developed to ascertain how this capitation program compared financially to a capitation rate based on the institution's current income. Once the framework for the model was agreed upon, the need was clear for utilization and financial data, appropriately defined. In this medical center a social research component in the Department of Community Medicine—the Office of Applied Social Research—had developed a historical data base derived from administrative data. This data base was able to provide information on the utilization of services by those patients to be included in the proposed program.

Organizational Impacts of Participation. At the medical center, the case manager approach was not consistent with some aspects of current clinical teaching and research practices, for several reasons.

First, the case manager's role was that of coordinator for patient care. As such, he or she would become a "gatekeeper" to other clinical services, controlling patient referrals and hospitalizations. This model, focused exclusively on patient care, ignored the medical center model, in which patients are research and clinical teaching subjects as well as patients. Further, medical center clinics are focused on the specific disease or condition of the patient and do not routinely provide continuity of care through a primary caretaker. The case manager approach conflicts with this specialty orientation.

The second inconsistency was the staffing structure in the outpatient clinics and the Emergency Room. The majority of hands-on care in these areas is provided by residents in training, supervised by attending physicians. The residents are usually on short rotations in a particular setting. The duration of the rotations and the degree of supervision may conflict with program requisites; thus, the integration of residency training and PPDP case management requirements would be difficult to achieve. It was apparent that if the medical center participated in the program, some reorganization in service delivery would be necessary to conform to the specifications of the proposal. Although this would vary with each department, in most cases it would be very difficult to implement.

Finally, although the PPDP case manager concept would place greater accountability for patient care on a primary care physician, in reality this control would often be diluted by specialists and residents who would not give this orientation the priority required by PPDP. The task force members did not consider it realistic to expect many of the educational and clinical practices of a medical center to change radically because of a small demonstration project.

An examination of the other requirements in-

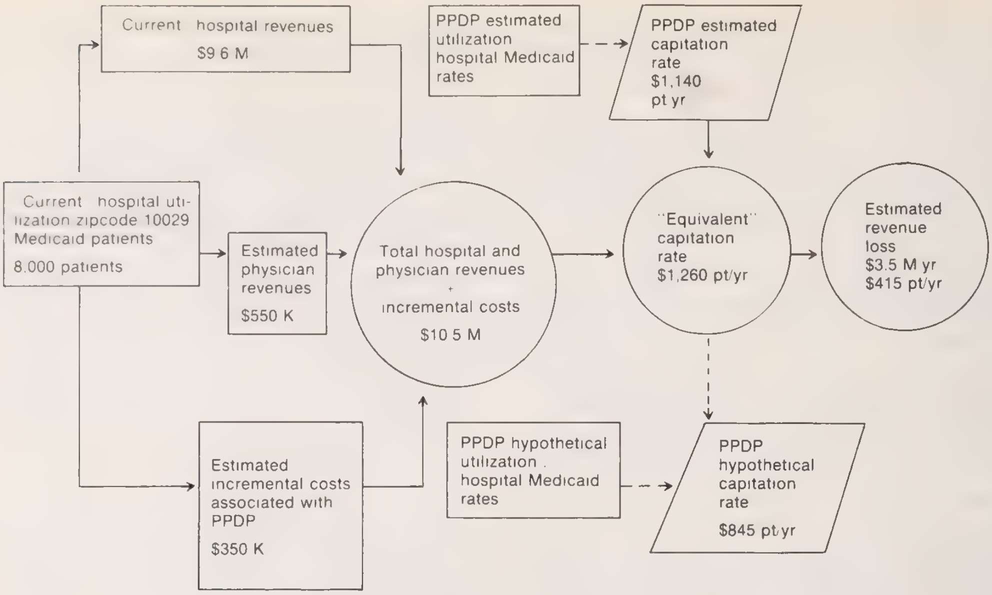
Current hospital revenues
$9 6 M
PPDP estimated utilization hospital Medicaid rates
PPDP estimated capitation rate
$1,140 pt yr
Current hospital utilization zipcode 10029 Medicaid patients
8,000 patients
Estimated physician revenues
$550 K
Total hospital and physician revenues + incremental costs
$10 5 M
"Equivalent" capitation rate
$1,260 pt/yr
Estimated revenue loss
$3.5 M yr
$415 pt/yr
Estimated incremental costs associated with PPDP
$350 K
PPDP hypothetical utilization hospital Medicaid rates
PPDP hypothetical capitation rate
$845 pt yr

Fig. 1. PPDP Participation: Financial Model

dicated that the medical center could assure 24-hour access to care for PPDP patients via the Emergency Room, and meet most general PPDP requirements. Difficulties were anticipated if patients who enrolled with another provider came to the Emergency Room for service. Under the terms of the proposal, these patients would be referred to their "appropriate" case manager at another institution. The legal, financial, and ethical ramifications of such referral practices would be onerous.

In Pediatrics, the possibility of full-time attendings functioning as case managers was questionable. Currently, residents under supervision provide these services during a 3–5 week assignment as part of their rotation. Furthermore, two additional pediatricians who would function exclusively as case managers were considered necessary.

In Obstetrics, physicians would have great difficulty meeting the case management requirements. These outpatient clinics are staffed by a combination of residents, full-time attending physicians, voluntary attending physicians, and midwives. Although all services are supervised by a board-certified attending physician, most care is provided by residents whose rotation is approximately two months. The service does not have attending-physician coverage for deliveries of patients attending the prenatal clinic, with the exception of some cesarian-section deliveries. One additional obstetrician would be required if the Medical Center participated in the proposed plan.

Furthermore, the preventive requirements of the proposed plan and the proposed patient utilization seemed contradictory. Obstetrical patients in the designated geographic area are a high-risk population, for whom underutilization of services is a major problem. Any program that improved prenatal care would probably (a) increase prenatal visits, (b) increase prenatal hospitalizations to prevent and/or treat prenatal complications, and (c) increase antenatal procedures (ultrasound, amniocentesis, laboratory tests). Thus, the PPDP goal to reduce the number of deliveries associated with late or no prenatal care would be likely to *increase* the utilization rates of this population and push up the cost of such care. The PPDP program goals and requirements would be thwarted by the program's reimbursement structure.

In Medicine, a private group practice, Internal Medicine Associates, which has replaced the general medical clinic, would be an appropriate provider of case management. The group practice consists of six attending physicians who supervise teams of residents and nurse-practitioners. However, a problem would arise in the continuity of care and management of patients because the medical residents, not the group practice physicians, control admissions to the medical service. In addition, there is little control over referrals from the specialists once a referral from the group practice is completed.

In the Outpatient Department, the problems in meeting case management requirements in the clinics and Emergency Room were similar to those of other departments. In order to comply with the case-manager concept, greater communication would be required between physicians in the departments of Medicine, Pediatrics, and Obstetrics/Gynecology.

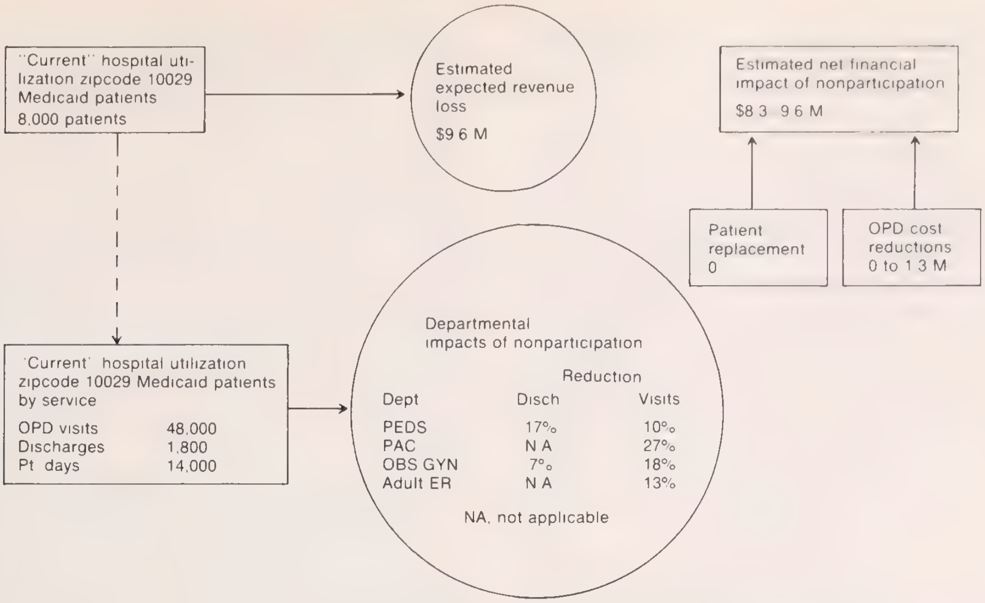
"Current" hospital utilization zipcode 10029 Medicaid patients
8,000 patients
Estimated expected revenue loss
$9.6 M
Estimated net financial impact of nonparticipation
$8.3–9.6 M
Patient replacement
0
OPD cost reductions
0 to 1.3 M
"Current" hospital utilization zipcode 10029 Medicaid patients by service
OPD visits 48,000
Discharges 1,800
Pt days 14,000
Departmental impacts of nonparticipation
Reduction
Dept Disch Visits
PEDS 17% 10%
PAC NA 27%
OBS GYN 7% 18%
Adult ER NA 13%
NA, not applicable

Fig. 2. PPDP Nonparticipation: Finance and Organization

Potential staffing increases would also be necessary to institute other required program features, including patient education, grievance procedures, intermediary relations, and elaborate quality insurance criteria.

Financial Impacts of Participation. The Primary Provider Demonstration Project as a capitation program would reimburse providers from a formula based on per capita utilization by six different categories of welfare recipients (Aid to Families with Dependent Children, Home Relief, and others). The per capita Medicaid rate depended on citywide utilization figures for each category. It was therefore necessary to ascertain what capitation rate the medical center would need to maintain current revenues.

This analysis focused on a comparison of revenues derived from current patient utilization and those developed by the city in its proposal. Incremental costs of the program and loss of physician fees were also estimated (Fig. 1).

"Current" patient utilization: To determine revenue generated by patients living in the designated area and reimbursed by Medicaid, the data specific to these patients was necessary. The resources of the in-house research unit, the OASR, were utilized to assess the use of services by Medicaid patients who received care in the hospital. All data was derived by patients, not visits or days. Direct data by patient is frequently unavailable in hospital statistics.

"Current" hospital revenues: Those current patients (approximately 8,000) living in the target area and reimbused by Medicaid were selected from the total hospital patient population. The "current" inpatient and outpatient revenues generated by these patients were estimated from data made available by the research office. Thus, patient days, clinic visits, and so on, for this specific subgroup of hospital patients were extracted. From these data, total "current" hospital revenues were estimated.

Estimated physician revenues and incremental costs: The fees that Mount Sinai physicians would receive for hospitalized Medicaid patients had to be determined for inclusion in the capitation rate. Estimates were made for admitting and consulting physicians' visits for the appropriate population of Mount Sinai inpatients. This included estimates for physician services in surgery, radiology, anesthesiology, and obstetrics. These estimates were multiplied by the appropriate average Medicaid fee. Finally, the value of certain incremental costs which would be incurred to comply with the proposed program requirements was also estimated.

Capitation rates: To compare current revenues with those anticipated by the proposed program, we calculated an equivalent capitation rate by dividing total revenues by the number of patients from the designated area who used the hospital in the previous year. It was assumed that the number of patients would be consistent.

The proposal described two distinct provider capitation rates based on enrollees' use of services. The first, "PPDP estimated capitation rate," used historical data on utilization by Medicaid patients in the designated zip code. The second used target utilization for the same population and was termed the "PPDP hypothetical capitation rate." Because capitation rates were based on six welfare categories for Medicaid patients, utilization for each enrollee category was multiplied by the hospital's Medicaid reimbursement rate to arrive at the average capitation rates.

In summary, based on utilization revenues for the designated population currently utilizing medical center services, the task force estimated an equivalent capitation rate for the hospital at $1,260 per person per year, as compared to a capitation rate based on utilization rates for the entire designated population of $1,140 ("PPDP estimated capitation rate") and a "PPDP hypothetical capitation rate" of $845. Since one of the objectives of the PPDP was to reduce utilization and thus save Medicaid expenditures, it was considered likely that the hypothetical rate or a variation of it would be put into effect.

Based on the analysis of revenues and incremental costs associated with participation, the Medical Center could lose as much as $415 per patient per year, or approximately $3.5 million annually. Finally, it was important to remember that although the stated intention of the proposal was reduced utilization, a program to encourage better prenatal care would in fact increase it. Reduction of costs and improvement in quality were still not reconciled.

Organizational Impacts of Nonparticipation. If the proposed program were implemented and the medical center chose not to participate, a significant patient loss would occur. The 8,000 patients in question accounted for approximately 14,000 patient days, 1,800 discharges, 8,000 Emergency Room visits, and 40,000 clinic visits. It was especially clear that these patients were heavy utilizers of clinic and Emergency Room services (Fig. 2).

To understand the full effect of nonparticipation, each service was reviewed separately. In general, the impact on inpatient services was less severe than on outpatient services. The reduction in outpatient visits was particularly high for Pediatrics (10%), the Pediatric Acute Care Clinic (27%), and Obstetrics (18%). Several other outpatient services would also be affected. The impact on the inpatient services was less significant. Obstetrics would lose about 7% of its discharges. However, the loss was high for Pediatrics (17% of discharges) and the Adult Emergency Room (about 13% of visits). Such a large loss in the patient care component could affect some departmental training programs.

Financial Impact of Nonparticipation. With nonparticipation, lost inpatient and outpatient revenues generated by the 8,000 patients in question would cause an estimated expected revenue loss of $9.6 million annually. The possible mitigating factors were patient replacement and cost reduction. The analysis assumed that these "lost" patients would not be replaced. A range of cost reduction was estimated, to arrive at an estimated net financial impact (revenue loss) of $8.3–9.6 million.

Task Force Recommendations. Based on the analysis, the task force recommended that the medical center not voluntarily participate because of adverse organizational and financial impacts. However, if the program were implemented unilaterally by the city, nonparticipation would not be a viable option. The following steps were therefore recommended:

- The medical center should provide New York City officials with suggestions for modifications to the proposal that would make it feasible for the medical center.
- The medical center should further evaluate the necessary steps to reduce the negative effects of nonparticipation in a capitation program. In anticipation of this, further analysis of the patient replacement issue and cost reduction would be useful.
- It was believed likely that some form of capitation legislation would be enacted by the New York State legislature. Because a capitation program is complex and would require major organizational changes, more collaborative planning should be encouraged between provider and reimbursement agencies.

Program Enhancements. The impact analysis was based on information and specifications outlined in the city's proposal. The task force was also interested in introducing changes into the proposal itself. Several ways to improve the proposal were suggested:

- Because appropriate prenatal care would be likely to increase utilization, a separate capitation rate for prenatal care was suggested.
- Enrollees should be given the option to receive a second opinion from another physician who could be from another institution.
- Because the medical center offered many specialty services, it may have been selectively drawing the most ill patients from the target area. The utilization rates of the total target population were lower than those of the medical center for the patients from the same target population. To reduce the institution's financial risk, the medical center should be allowed more flexibility to market the capitation program to a portion of lower utilizers. This is in keeping with the underlying concept that capitation providers act as

their own insurers in order to spread the risk. A revised formula for enrollment would need to be mutually agreed on by all PPDP providers.

- Because of the difficulties in controlling emergency room utilization for nonenrollees, visits to the ER should not be incorporated into the capitation rate. This is similar to other HMO policies. Another alternative would be a "pool" of money to reimburse providers when an enrollee receives emergency care at an institution that is not the designated provider.

Conclusions. The impact analysis of the medical center's participation or nonparticipation in the proposed program provided realistic information to senior management to aid their decision making. As the task force had anticipated, in mid-1984, the Governor's Medicaid Reform Bill was passed by the New York State legislature. The act called for seven capitation demonstration projects for Medicaid enrollees in various locations in the state. Most critical for the target populations, compulsory sign-up was excluded from the legislation. The New York State demonstration program precluded the necessity of immediate action on the PPDP proposal.

The PPDP analysis succeeded in accomplishing three important goals. First, it provided a cogent examination of the key PPDP impacts. Second, it lay the groundwork for subsequent studies on capitation programs by clearly identifying a segment of Mount Sinai's Medicaid population and by citing the strengths and weaknesses of a case management program at an academic medical center. Third, it clearly illustrated the successful application of health services research for planning specific institutional needs and decisions.

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Development and Application of a Productivity Data Base for Hospitals

C. Douglas Kundel, B.S.

Abstract

Salary expenses, staff levels, and productivity are vital to hospital operating budgets. The Operations Reporting System Data Base can compare departments in different institutions and forecast impacts of anticipated changes using departmental operating characteristics rather than traditional bases (institutional size, geography).

The preponderance of advances in medicine have been made in the twentieth century; at the same time a system of health care delivery of tremendous proportions has been created. Today in the United States, an estimated one in five employed persons works in some health-related job. Many of these people are employed in the private sector, in physicians' offices, manufacturing, or medical supply sales, for example; but many others are employed by acute-care and long-term care facilities supported by tax dollars and insurance premiums as well as by personal income.

In the past twenty years unprecedented increases in the cost of running hospitals have prompted both the public and the private sector to become increasingly alarmed at and involved in efforts to control the cost of health care. For instance, several Fortune 500 companies who pay employee health benefits are holding hospitals responsible and accountable for the cost of services rendered, working through executives on hospital boards of directors, through direct investment, or through union negotiations. This is reasonably easy in those geographic areas in which a factory is the area's largest employer and therefore a major source of revenue for the local hospital. Another method of cost containment is the use of DRGs (diagnosis-related groups) as a mechanism for determining reimbursement; a hospital will be paid $X for a given patient's hospital stay, based on a classification of the patient's disease and its cost. If the cost of delivering care is more than the DRG reimbursement, the hospital loses money on that patient. By the same token, hospitals can realize a profit if they can deliver the expected level of care at a cost below the predetermined fee (see Burick D, Duvall TJ, "Hospital cost accounting: strategic considerations," *Hospitals,* May 1985).

Regardless of the source of the pressure, hospitals have become more and more conscious of the need to control operating costs. While it is not the intent of this article to ponder the fate of "non-cost-effective" hospitals, virtually every facility's management, be it a board of directors or a chief executive officer, is acutely aware of the pressure and is concerned that it be squarely and decisively dealt with.

Productivity was not much of an issue in the hospital field until 1966, when Medicare was first introduced. Ever since that time, third-party reimbursement in a variety of forms has loomed large in determining each hospital's income. Early forms of Medicare reimbursement were relatively simple: hospital revenue was directly related to expenses; whatever it cost to provide care was what was paid. More recent forms of reimbursement, DRGs being the most recent and the best example, have set strict limits on reimbursement revenue. Although certain allowances are made for variance in expenses, it is primarily up to the facility to control its own expenses.

Because payroll expenses represent such a large segment of a typical hospital's expense budget, health care professionals are acutely aware of the importance of productivity as a vital management issue. Approaches to the issue have ranged from that of traditional management en-

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gineering to more recently prevalent comparative systems.

Management Engineering. Initially, the management engineering approach, still widely used throughout the industry to seek efficient and effective methods by which to accomplish a given task or job, was to use tried and true management-engineered work measurement and incremental time standards in the hospital setting. The results were successful; a variety of methods enable management engineers to establish an accurate "manhours per unit of measure" standard for most ancillary, nursing, and support departments in a hospital. Such standards are typically used retrospectively, to compare required with actual staff, and prospectively, to budget payroll expense, to forecast staffing needs based on projected workload volumes, to schedule shifts, and to allocate vacation, holiday, and sick time. When developed and applied properly, engineered standards are widely accepted; however, they provide the administrator or manager a comparison only with his or her own operation, at best with a set of numbers derived from the "stopwatch-and-clipboard" routine. Determinations that an institution was overstaffed or understaffed were limited in value because no larger context was available.

Data-Based Comparisons. In recent years, however, comparative data bases incorporating past research and current information have become available. Most systems compare a given hospital's productivity, by departments, with similarly sized facilities; with facilities in the same geographic areas; with other teaching or nonteaching facilities; with other urban or rural facilities.

Although each of these comparisons provides a valuable benchmark, none offers much insight into alternatives that would ensure either improved productivity or—at the least—cost avoidance. Furthermore, regulations that exert external pressure on hospitals for tighter management and cost control continue to multiply:

Regulations requiring changes in the methods by which patient care is rendered (such as New Jersey State requirements that all hospital pharmacies implement unit dose medication distribution systems).

Requirements by virtually all third-party payors with respect to data (such as New York State's SPARCS data base).

Technological improvements that either necessity or market forces are thrusting on most facilities (such as CAT scanning, data processing systems).

In consideration of limitations in existing data bases and in response to the rapidly changing environment, Management and Planning Services (MAPS), the consulting arm of the Hospital Association of New York State, came to view its accumulated productivity research data in a very different light.

Comparing Functions. It was MAPS' conclusion that staffing needs and productivity are determined more by *what* functions are performed and *how* those functions are performed than by how large a facility is, where it is located, and so on.

For example, if a hospital administrator were to compare his pharmacy's productivity with similarly sized, urban teaching hospitals, he might find that his pharmacy operates at .212 manhours per patient day (MH/PD); but using a 20-hospital group for comparison, the range might be .150 to .215 MH/PD. From this baseline data, he may conclude that his pharmacy is not productive in comparison. Consequently, he may take action to improve productivity by reducing staff, or channeling extra work through the department. However, these measures may prove to be inappropriate when further analysis is conducted. If, upon further investigation, the administrator finds that of those 20 facilities surveyed, only his and the facility operating at .215 MH/PD had full unit dose medication distribution systems and comprehensive intravenous additive programs (both of which are labor-intensive), the picture changes dramatically. The ability to compare his pharmacy to others that have the same basic operating characteristics provides better information on which to base decisions. He may find that within this new comparative group, the range of manhours per patient day is .209 to .232, which puts his hospital in a very different and more favorable position than in the first comparison.

The reasoning evident in this example prompted the development of MAPS' Operations Reporting System Data Base.

The Data Base. The Operations Reporting System (ORS) Data Base is designed specifically to provide or display empirically derived data in a format allowing accurate baseline comparisons. Stated simply, ORS compares apples with apples. What makes the ORS a unique productivity monitoring tool is that all the data in the system is stratified by definitions based on the operational system. For every facility which submits data, each department is coded as falling into one of several predetermined categories. Each category comprises a specific group of functional or operational characteristics.

To continue the example of the hospital pharmacy: A hospital pharmacy is assumed to be responsible for a wide range of activities. During the approximately twelve years in which data have been accumulated and pharmacy studies conducted, MAPS has observed that certain basic functions or responsibilities have the most significant impact upon staffing requirements in pharmacies, including such tasks as:

- Dispensing drugs and pharmaceutical supplies to patients, to certain functional units, and to employees authorized to receive such services from the hospital.
- Monitoring drug therapy through the use of a direct copy of the physician's order forms and of patient profile cards.
- Delivering drugs to designated areas in the hospital.
- Developing and compiling records and procedures for inventory control and for proper determination of drug charges to patients and to functional units of the hospital.
- Requisitioning and/or purchasing drugs and pharmaceutical supplies for the hospital.
- Receiving and storing drugs and pharmaceutical supplies.
- Compiling, storing, retrieving, and disseminating drug information.
- Educating, training, and briefing the hospital staff on pharmaceutical matter.

Although the tasks are assumed, the methods by which they are accomplished are not. Questionnaires completed by hospital staff identify the unique operational characteristics of each department. In addition, actual paid staffing levels and workload (unit of service) volumes are also included. When the questionnaires are edited and entered into the data base, each department is coded as a particular type of operating system. For instance, a pharmacy coded as having a unit dose system, computerized patient profile, and a completely centralized intravenous additive program would be compared only with others having the same characteristics. Today over 300 facilities report data in the ORS data base. Although most are from the northeastern quarter of the United States, a number of others are sited across the nation.

In addition to the classification by operational system, distinctions are also made between rural and urban, and teaching and nonteaching facilities. At present no case-mix intensity or DRG information is accumulated. However, such a delineation is the next logical step.

Applications. Hospital administrators face a future of challenge and change. One of the greatest challenges is to control operating expenses in an economy fraught with spiraling inflation, increasing prices, and growing wage demands. This environment has led many decision-makers to the realization that productivity is a key issue. Frequently, the questions that result from this realization take the following form:

- Is my hospital productive, department by department, compared to my counterparts?
- Are there methods or systems available that would improve our productivity?

Historically, the answers to these questions were either elusive, or costly, or both. Elaborate and expensive management engineering efforts, coupled with detailed cost-benefit analyses, were required. Even so, useful answers were not necessarily forthcoming.

The ORS is intended to provide accurate guidelines in a timely, cost-effective manner.

The Operations Profile. The basic profile for decision-makers is created as follows:

A detailed questionnaire is completed by hospital administration, describing the operating characteristics of each department. Related information is collected as well (for example, budgeted staff by department, unit of service or workload volumes).

The questionnaire is edited for accuracy and completeness.

Each department is classified into one of the predetermined stratified categories.

The data are fed into a computer to produce the operations profile.

Comparing. The Operations Profile (Table 1) compares each department's paid manhours per unit of service to the productivity range established for all departments having the same operating system. The acceptable limit is one standard deviation from the mean of the reporting departments within the subgroup. Thus, 66% fall within this range. Those outside this range are defined as outliers.

A review of the Operations Profile shows that certain departments seem to warrant attention. The pharmacy, for example, is operating above the range of comparable pharmacies. Additional detailed analysis would be required to clearly determine if overstaffing is the issue and, if so, at what skill levels and functional areas. Nevertheless, the profile can clearly be used to alert the administrator to problem areas and to set priorities and goals. To control cost, an administrator may set a short-term goal for all departments to operate within the range of required manhours per unit of service. An administrator may also set a long-term goal that all departments fall within 10% of the median. The Operations Profile can monitor progress toward these goals.

TABLE 1

Operations Profile: Community Hospital, Anytown, USA

Department*	OS†	Unit of service‡	Actual volume§	Actual FTE	Paid hrs/US¶	Ranges: Required paid hrs/US# Low	Ranges: Required paid hrs/US# High	Ranges: Required paid FTEs** Low	Ranges: Required paid FTEs** High	Above/below range††
Ancillary/Support										
CSS	E	Pt days	107,124	13.4	0.2603	.02411	0.3129	12.4	16.1	
Purchasing	B	Pt days	107,124	7.5	0.1461	0.0848	0.1032	4.4	5.3	A
Distrib/Stores	B	Pt days	107,124	6.4	0.1250	0.1573	0.2056	8.1	10.6	B
Total				27.3				24.9	32.0	
Cafeteria	A	Cafe meals	103,906	10.8	0.2169	0.1120	0.1859	5.6	9.3	A
Dietary	C	Pt meals	281,839	45.0	0.3319	0.3808	0.4687	51.6	63.5	B
Total				55.8				57.2	72.8	
Medical Records	A	Discharges	15,881	28.4	3.7185	2.9157	3.6322	22.3	27.7	A
CT Scan	A	Procedures	5,194	6.8	2.7301	1.7824	2.7865	4.5	7.0	
Radiation Therapy	B	Procedures	15,374	12.3	1.6634	1.1698	1.6546	8.6	12.2	A
Nuclear Medicine	A	Procedures	3,938	3.2	1.6699	1.6803	2.9318	3.2	5.6	B
Ultrasound	A	Procedures	5,832	3.1	1.0880	1.3010	1.6156	3.6	4.5	B
Diagnostic Radiology	B	Procedures	53,794	36.2	1.4010	1.2171	1.4814	31.5	38.3	
Total				61.6				51.4	67.6	
EKG	A	Procedures	22,200	10.4	0.9746	0.6406	0.9237	6.8	9.9	A
Respiratory Therapy	A	Procedures	50,973	15.0	0.6102	0.5902	0.7452	14.5	18.3	
Pharmacy	D	Pt days	107,124	23.5	0.4278	0.2983	0.3944	15.4	20.3	A
Total				48.9				36.7	48.5	

* Each department for which data comparisons are available has been included in the report.

† OS, Operating system definition code. Letters stand for operating system of the department. The code identifies the departmental stratifier utilized by the Operations Reporting System data base for the productivity reference range.

‡ For each department, a statistical measurement for workload (visits, patient days) is selected. The productivity of a given department is measured against fluctuations in this unit.

§ Actual 1983 reported workload.

‖ Actual paid staff in terms of full-time equivalents (FTE).

¶ Paid hours/unit of service (PH/US): actual paid hours per unit of service; (actual paid staff × hours paid per FTE) divided by (appropriate unit of service volume) = Paid hours per unit of service (PH/US).

Range of paid hours per unit of service (PH/US). Productivity reference range from the Operations Reporting System (ORS). The ORS data base contains a vast array of information on hospital departments. Productivity reference ranges are not utilized until the data elements for a particular department constitute a statistically significant sample.

** Range of paid FTEs required to maintain operations of each department, given workload experienced by hospital during period in question (typically one fiscal year). Productivity reference range × annual workload ÷ annual paid hours/FTE = required paid FTE.

†† A, above acceptable range; B, below acceptable range.

Forecasting. In addition, the ORS data base can be used to project or forecast changes in departmental responsibilities and/or workload.

Let's assume that the pharmacy uses a traditional medication distribution system and will implement a unit dose distribution system on completion of a building program. The building program will add 25 beds to the hospital's existing bed complement. The change in systems and workload will have a dramatic effect on the pharmacy. Recomputing the Operations Profile (Table 2) can provide baseline information on that effect.

The patient day workload volume is higher, and a different comparative group (pharmacy *with* unit dose medication distribution system) is used. Table 2 shows that the change in systems and workload will increase staffing requirements

TABLE 2

Pharmacy Comparison: Community Hospital, Anytown, USA

Department	OS	Unit of service	Actual volume	Actual FTE	Paid hrs/US	Ranges: Required paid hrs/US Low	Ranges: Required paid hrs/US High	Ranges: Required paid FTEs Low	Ranges: Required paid FTEs High	Above/below range
Pharmacy (existing)*	D	Pat. Days	107,124	23.5	0.4278	0.2983	0.3944	15.4	20.3	A
Pharmacy (projected)†	B	Pat. Days	115,337	23.5	0.4238	0.3612	0.4400	20.0	24.4	

* Traditional medication distribution system.

† With additional workload (25 additional beds at 90% occupancy for one year = 8,213 added patient days), compared to pharmacies with unit dose systems.

in the pharmacy (a unit dose medication distribution system is typically more labor-intensive than a traditional one, as evidenced by the higher range of required manhours per unit of service). Although an increase in *required* staffing will result, the profile indicates that current or actual staffing levels can absorb the added workload and operate the unit dose system. The pharmacy will be more productive as a result of the changes. Again, additional detail is required for skill level adjustments, hours of coverage, and so on, but the comparison provides a much-needed starting point for structured and effective decision making and policy formulation.

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Constraints in the Development of a Rural Primary Health Care Program in the Dominican Republic

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Abstract

Since 1979, the Mount Sinai School of Medicine (NY) Department of Community Medicine has provided technical assistance in the development of a primary health care system in the Dominican Republic. This paper describes research activities for the project, their use, and institutional constraints and support for their application.

Since mid-1979, the Mount Sinai School of Medicine Department of Community Medicine has provided technical assistance to the Gulf + Western Americas Corporation in the development of a rational and effective primary health care delivery system for a defined population in the Dominican Republic.

The Gulf + Western Americas Corporation, a subsidiary of Gulf + Western, operates a sugar plantation and sugar mill in the southeastern section of the Dominican Republic. A permanent population of approximately 40,000 workers and their families, together with 10,000–15,000 migrant workers, are involved in planting, caring for, and harvesting over 200,000 acres of sugar cane. This rural population is dispersed among 105 villages of from 20 to 2,000 inhabitants.

To provide health care for this population, the Dominican Republic has a tripartite system: (a) a Department of Public Health and Social Welfare, which offers health care services to the entire population via a nationwide network of health centers and hospitals; (b) a Social Security Institute, which operates dispensaries and hospitals that serve all employed workers earning less than a specified amount per year; (c) a coexisting private, fee-for-service sector.

There are three Public Health clinics and nine Social Security dispensaries in Gulf + Western's operational area. La Romana, a city of 80,000 residents where the sugar mill is located, has a Public Health hospital, a Social Security hospital, and two small private hospitals.

Gulf + Western operates a small hospital for its employees in La Romana. In addition, since distances between government clinics are considerable and the clinics themselves are often undersupplied and understaffed, the company has for several years provided ambulatory primary medical services to rural residents via physician-staffed mobile units. By 1979, however, Gulf + Western executives had come to feel that the mobile unit program in its existing form could not significantly improve the health status of the population it was serving despite major financial outlays, and asked the Department of Community Medicine for technical assistance.

The department approaches technical assistance activities within an educational framework. Faculty members concentrate on training local leaders in problem identification, recognition and assessment of alternative solutions, program planning, and concurrent evaluation. The department avoids short-term, crisis-oriented consultancy, and does not at any time accept responsibility for direct services delivery (1, 2).

Data Collection and Planning. The first step in the Dominican Republic was generation of consensus on program goals. The Mount Sinai project director assisted the company's health care professionals to describe roughly the characteristics, geographic distribution, and health needs of the population to be served, and in this context to identify three broad, long-term goals:

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1. Development of a comprehensive, family-oriented program of preventive and curative health care for rural employees and their families.
2. Development of continuing education programs for the company's health care personnel (physicians, nurses, technicians, community workers).
3. Development of a program of applied research to assure the ongoing evaluation and refinement of the health plan and programs resulting from fulfillment of goals 1 and 2.

The Dominican planning group assigned the director of the Rural Health Program primary responsibility for the preparation of a rural health plan commensurate with these goals. During the earliest stages of program definition and planning, published national and regional Dominican vital and health statistics were reviewed and analyzed, as were relevant company records (including hospital and mobile unit utilization data), in order to more accurately and precisely describe the population to be served and its health needs. Existing public and private health resources—human, physical, and financial—were similarly identified and described.

A lack of morbidity data, an acknowledged under-registration of infant deaths, and the geographic classification of data primarily in national and provincial units made the available information inadequate for detailed small-area planning. The demographic composition of the rural population was unknown, and regional data on the prevalence of significant conditions such as venereal disease and malnutrition were often in conflict with the impressions of local health personnel.

In consequence, during the summer of 1980, a community survey of the rural population was conducted. Under the direction of the Rural Health Program Director and with on-site technical assistance from the Mount Sinai epidemiologist, a geographically representative cluster sample of 1,100 individuals was interviewed and examined. The age, sex, ethnic, and primary-language distributions, current health care utilization patterns, and perceived health of the population were ascertained through open-ended interviews. Each participant was given a directed physical examination, and blood, urine, and fecal samples were collected for laboratory analysis. The conditions of particular interest to the planning group were intestinal parasites, diarrheas, upper respiratory tract infections, otitis media and nutritional deficiencies in children, and pregnancy, venereal diseases, tuberculosis, hypertension, and malaria in adults.

The survey results showed a high prevalence of intestinal parasitic infestations, venereal disease, hypertension, and anemias. They provided statistical support for development of a health plan giving priority to health promotion and disease prevention activities. They also provided support for development of an integrated program to improve company-provided housing, sanitation, and health care services.

The prevalence of tuberculosis, malaria, severe (grades II and III) malnutrition and diarrhea in children were unexpectedly low. Rather than develop special education and screening programs focussed on tuberculosis and malaria, it was decided to limit program activities to support of ongoing government programs. A food supplement program for pregnant women and children was put in abeyance and plans for oral rehydration services were scaled down.

The nutritional findings (based on weight, height, and age measurements) were so completely contraintuitive that the likelihood of measurement error seemed great. In an attempt to resolve the issue, a second data-collection cycle was undertaken, with two components: (a) nutritional assessment of an age-stratified and geographically stratified sample of children 0–5 years of age living in the administrative area chosen as the site of the first health center, and (b) a survey of adult residents' health knowledge, beliefs, and behaviors re venereal diseases, intestinal parasites, malaria, tuberculosis, pregnancy, prenatal care, and infant care. The latter study was designed to identify those issues for which community health education programs would be required.

The nutritional assessment (anthropometric, clinical, and laboratory evaluations) confirmed the relatively low rates of moderate and severe malnutrition ($<10\%$) in this population. As a result the population-based diet supplement program was abandoned for a program oriented to nutrition education with direct intervention only in individual cases. The results of the beliefs-and-behaviors study led the planning team to strengthen and focus the educational components of the program, and to include a full-time health educator among center personnel.

The two research cycles provided the planning team a comprehensive data base tailormade to their needs. Because the researchers in this case were also members of the planning team, the researchers' interests and the planners' needs meshed perfectly, and research findings served to orient the developing primary care plan. The study results also proved extremely useful to the Dominican rural health personnel who had to convince their curatively oriented, hospital-based colleagues to accept a rural program that stressed education, promotion, and prevention rather than therapy.

Implementation. The plan devised by the joint Dominican–Mount Sinai team was accepted in principle by Gulf + Western's administration. Briefly, it provides for primary care services in each of seven health centers, together with simple laboratory services, pharmaceutical services, and emergency care. Referrals are made to appropriate providers for secondary and tertiary care. The plan introduced the concept of case management. Referral and follow-up procedures are defined to facilitate continuity of care despite the inherent difficulties of coordinating multi-institutional care. The plan clearly defines health promotion and disease prevention objectives and identifies the community outreach and organization required for their accomplishment. In addition to two physician-nurse teams, each center staff was to include a full-time health educator and a sanitation officer, who would together take primary responsibility for community education and organization in such issues as personal hygiene, nutrition, waste disposal, and immunizations.

The first center opened as a demonstration project in June 1982, in the most medically isolated sector of the company's lands. Despite nominal institutional acceptance, there were difficulties in implementing the complete program. Initially, only the curative services were implemented successfully; prevention and promotion activities were severely limited by institutional constraints.

Institutional Constraints. The traditional managerial and medical orientations of the company's executive and decision-making personnel combined with a number of external circumstances to militate against adherence to the full plan. Program approval and implementation coincided with a drop in sugar prices on the international market. This economic situation led G + W Americas Corp. to institute an austerity budget, one of whose effects was to reduce the amount of money available to invest in health care. Economic conditions reinforced the existing tendency to delay implementation of the least appreciated and understood elements of the new program: the functions and positions of the health educator and sanitation official. The situation became more difficult when the Rural Program director requested a leave of absence following his election to the Senate. His departure, for an undefined period of time, created an authority vacuum at the middle management level.

Having chosen not to become directly involved in service provision, the Mount Sinai team has no direct authority or power to implement the programs it helps to establish. The successful achievement of team objectives depends on the efforts of local personnel who share those objectives. The absence of the Rural Program director made it abundantly clear that the initial focus of staff development had been too narrow. Work with higher level administrative and medical staff had been less extensive than that with operational and field personnel. Although the former share the overall goal of improving health-related services, they did not recognize that achieving this goal would require significant changes in their usual modes of operation.

A health program stressing prevention and promotion involves a high proportion of activities (education, outreach, screening, disease surveillance, involvement in environmental improvement) not intrinsically medical. Recruitment and selection of physicians and nurses for a preventively oriented program must therefore not only be based on standard criteria, but must also involve assessment of these professionals' interest in, experience with, and motivation toward practice in a nonhospital setting that values community interaction and outreach activities as highly as in-center medical services. In La Romana, this implied a major change in administrative and managerial workstyles and a move away from traditional recruitment procedures toward selection of personnel on the basis of their ability to meet clearly defined sets of position-specific criteria. A related modification in attitudes was required to allow for inclusion of nonclinicians, such as health educators and sanitarians, as respected members of the center staff.

As might have been anticipated (3,4) the hospital medical director and administrator, who had assumed overall responsibility for program implementation, did not initially see the need for such alterations in their standard procedures. Because the norms and procedures of these institutional leaders remained disease oriented, physicians were selected who had no interest in rural primary care practice and who accepted service in the center only as a means to gain entry to the hospital practice that interested them. Nurses' aides rather than public health nurses were assigned to the center. Total center staff was reduced by elimination of the health educator and sanitarian positions. None of the staff members selected had any experience with community education or outreach programs, and except for the laboratory technician, none had any interest in them.

The watershed in program direction was due in fairly equal parts to (a) a deeply felt desire on everyone's part to see a change in the health status of the rural population, (b) the personal experience of failure to achieve this end via traditional means, (c) an ongoing educational campaign on the part of the consultants, and (d) serendipity. The technical assistance team, unable to exert direct authority, employed peer pressure and patience. The need to place a different type of individual in the key positions in the center as well as to augment the staff complement was stressed repeatedly in meetings with mid-level and high-level executives. Equal stress was placed on the importance of explicitly recognizing the significance of work in the rural areas and giving the work of professionals in these areas the prestige it deserves.

The resignation of several hospital physicians initiated and facilitated the process of staff changes by permitting transferral of the center's physician staff to the hospital positions they sought and their replacement by physicians with experience and interest in the development of a rural program with a preventive orientation. At approximately the same time, one of the nurse's aides resigned to get married. She was replaced by an RN-level nurse who had worked previously in community outreach programs in a rural setting.

The recruitment of a new director of the center and a more appropriately qualified staff has resulted in a highly visible boost in morale as well as expanded community and patient education programs. Among the first activities of the new center director were the institution of daily patient education sessions in Creole as well as Spanish, personal efforts to become acquainted with and involve community leaders in center activities, a series of community education programs held outside the center in the local community centers, and a complete review and summary of available data on center utilization patterns during its first year of operation. The planned anti-venereal-disease campaign has been initiated, and the prenatal and well-baby programs are being expanded in accordance with the original plan. The new medical director is attempting to expand the center staff to include a public health nurse to handle the responsibilities of the health educator and the sanitarian. He is using productivity data from the center's information system to justify his request for additional personnel, and initial reaction to the request has been favorable.

Discussion. The experience with the Romana project confirms Yankauer's observation: "The actual application of . . . plans on a community-wide basis is often the most frustrating aspect of the health services management process. Skepticism (in spite of demonstrated results), resistance to change in the customary ways of doing things, and vested interests in maintaining the status quo must all be overcome" (7). Assuring coincident interests among researchers, planners, and field staff; obtaining an adequate data base; and devising a detailed and economically feasible plan to meet identified needs are not sufficient to assure that necessary program modifications will take place. The extensive communications and educational needs of the final decision-making group must also be addressed if planned change is to occur.

In this instance the problems arising from traditional attitudes to health care delivery and heavy dependence on a single individual to secure program implementation and institutionalization might have been foreseen and steps taken to reduce their impact. Efforts on the part of the technical assistance team to foster an environment favorable to the new approach, and to prepare the professional staff most likely to be involved in day-to-day program operations, could and should have begun earlier and been more broadly based. Creation of the appropriate environment would have required that the executive leadership not only be familiar with and approve the plan but that they also understand the need for change, the nature of that change and its potential impact on them (5, 6). Under these conditions, the executive staff might have become more willing and able to alter its own workstyle, norms, and procedures so as to support the field staff and facilitate realization of program goals.

At the same time, the importance of personal experience with the practical need for change cannot be overemphasized. It appears to be human nature to alter behavior only when the need is actually felt rather than identified by others. The experience of failure when the usual operational mode was employed and the fear that such failure might have a negative career impact may have been necessary preconditions for acceptance of the modifications in institutional procedures required to bring about the changes desired in the rural program (7). Such experiential learning will undoubtedly continue to play an important role in the evolution and long-term institutionalization of the rural health care services plan.

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The Role of Social Scientists in Planning and Implementing Change in a Medical Center

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Abstract

We describe the role of a group of social scientists in planning conversion of a general medical clinic to a hospital-based primary-care group practice.

Planning change in an academic medical center is a difficult and complex process. Typically, planners, providers, and administrators collaborate to plan the design, to study its feasibility, and to predict the impact of the proposed change.

This paper describes the contribution of a group of social scientists in planning the conversion of a general medical clinic to a hospital-based primary care group practice. The social scientists, through their training in the analysis of social aggregates and groups, have the tools to study "the system of interrelated attributes that characterize the organization itself rather than its component parts" (1).

Whereas the planners were mostly concerned with the design and feasibility of the new model, the social scientists honed in on the issues they considered of major importance for a successful conversion— issues arising from the relations between segments of the institution, and the way those relationships would change.

Critical Issues in Planning

Background. Like many other urban hospitals, Mount Sinai was concerned about the increasing demand for primary care from its local low-income inner-city users (2). Its multitude of clinics produced a web of multiple visits, often duplicating effort and expense. Like other teaching hospitals, Mount Sinai was organized and staffed to deliver episodic care provided mostly by housestaff and loosely organized physicians (3–5).

To meet the needs of this segment of the population more appropriately and cost-effectively, Mount Sinai began to explore alternate ways in which more comprehensive, continuous care could be provided with more efficient use of resources (6). One of its efforts was the establishment of a multidisciplinary planning committee in 1978, to study the feasibility of and design a model for a hospital-based medical group practice to replace the existing General Medical Clinic. Two years later, a grant from the Robert Wood Johnson Foundation allowed implementation.

Identifying the Relational Issues. In the social scientists' view, the replacement of an existing service by a new mode of practice raised three critical issues:

1. Which clinic patients would be appropriate for the new group practice? The group practice was expected to provide coordinated, continuous, high-quality medical care to adults of all socioeconomic levels, including private patients. Such an expansion in scope of service might change the type and volume of patients treated in the group practice compared to the medical clinic.
2. What effect would the new group practice have on the remaining ambulatory-care clinics? The General Medical Clinic was a central channel for referral of patients from the emergency room to medical specialty and subspecialty clinics. With its removal, a major link in the formal referral system would disappear, threatening the existing flow of patients to the specialty clinics.
3. What effect would the group practice have

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on the availability of medical beds? If the group practice was going to become financially independent of the hospital, it needed to offset its lower medical reimbursement fees with a healthy patient mix of private patients in addition to the clinic population. This put the group in competition with the voluntary attendings for access to scarce medical beds.

Thus, predicting patient volume and use patterns was critical.

Finding a Data Source. The Office of Applied Social Research had drawn "an annual 10% random sample of patients from different hospital computer files . . . for analysis geared toward questions relevant to hospital management and planning" (7). These separate data bases had been integrated and now served the social scientists to shed some light on the intricate network of patient flow and utilization patterns before, during, and after implementation.

Issue 1: Predicting Patient Volume. Outpatient statistics for 1978 showed that 6,300 patients had made 18,900 visits to the General Medical Clinic (GMC). Would these patients be appropriate for primary care in the group practice, and would their visit volume remain the same?

The planning committee, primarily the physicians, felt comfortable with the GMC patient count as a baseline for patient demand. However, because they expected a change in patient behavior consistent with group practice exerience, they applied utilization figures from the Kaiser Permanente groups to the GMC patient count.

The social scientists suggested another approach. The Ghetto Medicine Bill's requirement that every patient have a primary physician had channeled outpatients through primary clinics such as the GMC. As a result, the GMC served two major functions: it provided treatment, and it acted as a triage for the specialty clinics. However, no information existed to account for these dual functions. For operational purposes it is sufficient to account for clinic activities and expected clinic income. The GMC figures conveyed only the volume of care provided in the GMC, not the type or extent of treatment GMC patients received within the hospital system.

Differentiating primary- and specialty-care volume: The social scientists wanted to establish through further analysis how many of the patients seen in the GMC were simply referred for specialty care and how many received their main treatment in the GMC.

To throw some light on this issue, the social scientists prepared a matrix which related the number of GMC visits to the total number of visits a patient made to the Outpatient Department in 1978. About one quarter of the GMC population comprised patients who had either used the GMC exclusively or who had made only one additional visit to another clinic. These patients would obviously qualify for the group practice. The remaining 75% were indeterminate as specialty clinic or group practice patients. They could have been primary-care patients referred to other clinics for consultation; they could also represent specialty-care patients for whose care the specialty clinic assumed responsibility.

A classification system was needed to distinguish specialty-care and primary-care patients. The social scientists conferred with the director of the group practice, who defined a primary-care patient for the group practice model as a patient with a ratio of no fewer than two GMC visits for every specialty clinic visit. Using this definition, the social scientists divided the patients who attended the GMC in 1978 into primary- and specialty-care groups. More than half of the GMC patients (57%) turned out to be primary-care patients; 43% were specialty-care patients.

The use of this classification was supported by the different utilization patterns in each group. As expected, primary-care patients accounted for the majority of visits to the GMC. They contributed 62% of the visits, compared to 38% contributed by the specialty-care patients. The difference was even more pronounced in their specialty-care use. Primary-care patients accounted for only 11% of the specialty clinic visits; specialty-care patients accounted for 89%. Furthermore, primary-care patients required less than half as many hospitalizations (12%) as specialty-care patients (27%) and averaged shorter stays.

Based on the number of GMC patients and their utilization patterns, 3,600 patients qualified as primary-care patients. They represented the core of patients for treatment in the group practice. Still at issue, however, was how many more patients would be absorbed through the expanded services of the practice, and how this would in turn affect other clinics.

Referrals: Mediating Potential Conflict. The GMC population averaged 11 ambulatory visits in 1978: 3 to the GMC and 8 to other outpatient areas. The large proportion of visits to other areas indicated the pivotal role the GMC played in follow-up and referral. In fact, only 13% of the GMC patients had been seen exclusively in the GMC; the remaining 87% had visited up to 17 additional clinics.

Implicit in the new service model of the group practice were fewer referrals, with potentially detrimental effects on the teaching and research protocols of the specialty-care clinics. For example: in the new model, unless a patient was severely hypertensive and more appropriately managed in the specialty clinic, he or she was not expected to be sent to the Hypertension Clinic. Under the old system, all patients with hypertension were referred for treatment to the specialty clinic. At this point the new group practice model and the institutional clinic model came into potential conflict. It was therefore essential to identify those clinics which would be most vulnerable to a change in referrals.

As a first step, the social scientists established the extent of ambulatory care sought outside the GMC. Almost two thirds of the GMC population had used the Emergency Room, often in lieu of a primary-care source as a convenient, easily accessible place for treatment of nonurgent conditions. Through personalized, continuous care, the group practice planned to absorb these patients and reduce their visits to the Emergency Room, benefiting both institution and patient. Over one third of all GMC patients were referred to the medical specialty and subspecialty clinics. Another surprisingly large proportion (28%) was sent to the psychiatric clinics. Gynecology and Ophthalmology each saw 19% of the GMC patients, Orthopedics 16%, Otolaryngology 15%, Dentistry 11%, and Neurology 9%. The remaining services accounted for 5% or fewer of the GMC patients.

The 23 medical specialty clinics were of greatest concern because they were the ones most directly affected by the change. To assess the impact of a group practice on these clinics, the social scientists established the proportion of GMC referrals in each. Overall, 11 of the clinics received more than half their patients through GMC referrals. But the range was wide: 21% (Myasthenia Gravis) to 91% (Nutrition).

Specialty clinics with a high rate of GMC referrals seemed more at risk from a conversion than those whose patient intake originated from a variety of sources. But other factors were important in determining the level of risk. Size plays a major role in determining the vulnerability of a clinic to referral changes; obviously, larger clinics can more easily absorb fluctuations than smaller clinics. Clinics such as Allergy and Asthma may shrink, but their existence is not immediately threatened.

Another factor is patient turnover. Clinics with a high patient turnover are more dependent on a steady flow of referrals than those with a low turnover and are therefore more susceptible to changes in the system. Although most of the smaller clinics had a high patient turnover, their existence was not threatened because of the nature and degree of their specialization. It became evident that the more general medical specialty clinics, which tended to be large, were most likely to lose patients to the group practice.

To avert future problems, the issue was discussed with the chiefs of the affected clinics. The medical chiefs expressed willingness to relinquish those patients who were not sick enough to require specialty care, in exchange for a smaller but more appropriate patient load. Anticipating the problem, addressing the appropriate chiefs, reviewing the risks, and arriving at a mutual solution avoided the misapprehension often arising from organizational change without communication with those potentially affected. As a result of the communication effort, this change was perceived as an improvement in clinic care, not a threat to the teaching and research protocols.

In summary, none of the medical specialty clinics were threatened by the conversion. Those that could be expected to lose patients were consulted, and a compromise resulted in a more appropriate patient load. Those patients who had used the Emergency Room as their primary source of care, and those who would no longer be referred to specialty clinics, could be expected to add 1,500 patients to the group practice, bringing the number of primary care patients to an estimated total of 5,000, based on careful analysis of the existing organizational structure.

Competition for Beds. To become financially independent from the hospital after startup, the group practice needed to attract private patients as well as the GMC patients to which it was committed. Without this financial independence, a large deficit could threaten its survival. However, provision of care to private patients would put the group practice in competition with the voluntary physicians. This was a dilemma for the planners.

This issue did in fact erupt into conflict. With the announcement of the group practice plan, the issue of access to beds became a high priority which had to be resolved. The voluntary attending physicians were concerned about the implications of the group practice for their own future role at the medical center. Out of their concern, they negotiated a constraint on the number of private patients and the number of beds that would become available to the group. With these restrictions, the competition for private patients and beds between the group practice and the voluntary attendings was greatly reduced. However, the restrictions inhibited the future opportunity for the group practice to become financially independent of continuing medical center support.

Implementation

Several issues were involved in the implementation of the new group practice, now named Internal Medicine Associates (IMA). As a demonstration project, the IMA had to provide evidence that a primary-care practice staffed by full-time physicians on a partnership basis was a viable alternative to the existing GMC, delivering care and supporting referrals to the ambulatory network of the hospital. Because of the many issues and parties involved in the conversion process, it was also necessary to monitor the schedule of the conversion and to make sure from the beginning that the population phased out of the GMC was actually absorbed by the IMA.

Monitoring the IMA Population. Keeping track of IMA's private and clinic patients required a uniform data base. The IMA was only partially integrated into the hospital system. GMC patients who were being seen at the IMA continued to be registered and billed by the hospital. However, private patients were excluded from this system. They had to be processed directly by the IMA. The social scientists convinced both hospital management and IMA of the necessity to include the private patients in a uniform identification system so that the total IMA population could be monitored.

One of the primary concerns of the IMA was to meet the Johnson Foundation's reporting requirements and IMA's own management needs. The social scientists, in collaboration with the medical director, developed a format for IMA's quarterly reports. These reports encompassed IMA's patient recruitment, visit volume, and physician activity, and in particular the private patient component. They also described the demographic and financial characteristics of the IMA population. The reports were routinely produced and distributed to all parties involved in the conversion process: the IMA group, the Outpatient Department, and the Department of Planning and Management Information Systems.

Annually, and additionally on request, the social scientists produced other reports. These provided assurance that visit decreases in the GMC paralleled visit increases in the IMA, and that the sociodemographic characteristics of the IMA population were similar to those of the GMC. The group practice was absorbing appropriate referrals in the conversion process.

Monitoring Physician Productivity. The hospital expected lower physician productivity in the IMA than in the GMC because the IMA was a private practice. However, when the conversion took longer than planned, and the IMA physicians seemed even less productive than expected, the hospital was not only worried about the timely phase-out of the GMC but also concerned that the new practice might be too expensive to maintain.

Initially the IMA was located in small temporary quarters; during this period IMA physicians were assigned sessions in the GMC. Analyzing IMA physician activities, the social scientists detected that the hospital forgot to include these services when it calculated IMA physician productivity. Further analysis revealed a discrepancy in visit recording. The IMA was not recording visits for medication refills, as was the practice in the GMC. Including their GMC activity and equating definitions of visits increased IMA physician productivity and brought it to a level commensurate with hospital expectations.

Monitoring Distribution of Private Patients among Providers. As long as the IMA remained a hospital-based group practice and received the hospital-based Medicaid rate, it had no need to worry about its patient mix. But the distribution of private patients among providers was important. The IMA derived a certain percentage of its income from services rendered to private patients. This income was divided among the providers according to a formula they had developed. It was therefore important that all providers participate in the services for private fees.

The social scientists developed data which showed the number of new private patients seen monthly by each of the providers. It turned out that only two of the three physicians and none of the nurse-practitioners were seeing private patients.

The reasons were explored. Private patients were either referred to the medical director, known to the medical center through his negotiations and meetings, or to a second physician acting as medical consultant to the Department of Psychiatry. The third physician and the nurse-practitioners had no outside exposure and were therefore not known to the clinical departments of the hospital. Once aware of the uneven distribution, the medical director instituted a procedure which insured greater equity of private-patient referral among the providers.

Monitoring Specialty Referrals. One of the physicians on the committee that planned the IMA had checked off a list of clinics most likely to be affected by the operation of the IMA. To assure the hospital and reassure the clinic chiefs of the specialty clinics that the IMA was continuing to refer patients for specialty care, in 1982 the social scientists analyzed the visit trend of all the clinics on this list.

Examining a three-year moving average from

1977 through 1981, it was clear that very few clinics underwent a change in visit trends concomitant with the operation of the IMA. Except for the GMC, whose visits decreased in proportion to the IMA's visit capacity, no obvious changes in visit trends occurred that could be attributed directly to the operation of the IMA. The changes that did show up were either cyclical or had begun a long time before the IMA opened, mostly as a result of the decreasing low-income population in the East Harlem area. This phenomenon included visits to the Allergy and Hypertension clinics. The report helped to alleviate fears that the IMA had stopped or changed referrals to the specialty clinics.

A study conducted in July 1984, shortly after the Robert Wood Johnson grant ended, showed that the utilization patterns of the IMA clinic patients had not changed significantly. Emergency Room and specialty clinic use and hospital admission rates of the 1983 IMA population closely resembled those of the GMC "primary-care" patients.

Discussion

The creation of a primary-care group practice to replace a traditional general medical clinic required a model based on knowledge of the population and utilization patterns of the traditional clinic. Once the new practice began, the medical center required an assessment of the impact of conversion on referral patterns to specialty and inpatient services.

Information required to plan and implement the conversion was unavailable from existing organizational sources. The social scientists took on the function of acquiring and analyzing data to provide this information. They defined specific organizational issues and prepared responses to them.

The social scientists were familiar with the organizational structure of the medical center's ambulatory care services and had to hand an integrated patient data-base which they had constructed. Using these resources, the social scientists explored and interpreted the various relationships between organizational components involved in issues the social scientists considered pertinent. Initially, the majority of those on the planning committee neither perceived nor understood the need for information on the referral network and the primary-care patient in the traditional clinic as a prerequisite for planning the group practice. Indeed, the physicians who dominated the planning process focused on the design of the practice model. They used a model modified from the Kaiser Permanente experience as a base to design a primary-care practice combining service, teaching, and research. As Rosenfeld has noted, "the majority of decisions the physician is called upon to make relate to norms of medicine in general and to practice in his specialty, and only in small measure to institutional policies" (8). The planning committee paid little interest to existing institutional structures and constraints.

The social scientists, on the other hand, were aware that an organizational change such as the conversion of a traditional medical clinic to a group practice would have a multitude of effects on the ambulatory care structure. As organizational analysts, they selected those effects that would have internal implications (9). Having the tools to analyze, clarify, and identify organizational issues, they viewed the group practice model in its organizational context, with all the ramifications that context entails. They thereby helped to predict the consequences of the planned intervention.

Researchers are often charged with being too isolated from institutional issues. The conversion of one form of clinic to another which we have described here is an instance in which the planners, primarily the physicians, focused almost exclusively on the future model, unaware of the vacuum the conversion created within the institution. The social scientists, on the other hand, paid special attention to the potential impact of the group practice on the remaining clinics in ambulatory care. Rowbottom has pointed out that "in collaborative exploration . . . the researcher no longer strives to avoid the influence of his own ideas and approaches on the subject. Indeed, he positively seeks to influence and affect those he is working with" (10). The analysis of the social scientists elucidated the relationship between the traditional clinic and other outpatient clinics and highlighted the different user groups in the referral process. The findings presented by the social scientists assured the planners that the group practice would offer positive benefits at minimal risk to the institution and to its clinic system.

The physicians did, indeed, worry about their peers' potential resistance to the group practice. They were aware that, in Donovan's words, "traditional medical staffs are uncomfortable with programs that are non-traditional in nature and not technologic in focus" and they knew that "the support of the medical staff would be difficult to achieve and its anxiety easy to stimulate" (11). They could have shared the information made available to them by using joint sessions to develop consensus and alleviate some of their colleagues' concerns (12). "The greater the costs, risks, and uncertainty, and the more significant the changes in methods and goals involved, the more intense is the search for information, but the stronger is the weight of established policy and vested interest" (13). Sharing information might have alleviated the fears that underlay the opposition to an unrestricted number of hospital beds for the IMA. Instead, the particular compromise reached on the issue forced the new group practice to restrict its size and, without a sufficiently large private patient base, remain hospital-dependent. Some other compromise solution might have been found.

During the implementation, the analysts helped identify effective strategies to reach the defined objectives of the group practice and to decide its future direction. "Failure in health planning is most commonly caused by inadequate attention to implementation. . . . [The] tendency to stay isolated from the facts of real life and the process of implementation is responsible for the commonly heard criticism that health planners tend to be impractical and their plan irrelevant" (14). The social scientists used their knowledge of the organization to identify issues critical to the integration of the group practice into the Outpatient Department, thereby helping to lay the groundwork for the acceptance and survival of the group practice. Their participation helped the collaborative process which finally achieved the goal of institutionalizing the group practice in the medical center.

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Communicating and Disseminating Results

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Research Settings and Health Services Research: Does Where You Do It Affect Who Listens?

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The influence of university-based research on federal and state health care policy has lessened under the present administration; research in professional associations, hospitals, federal, state, and local government units, employer organizations, consulting firms, consumer coalitions, and labor unions seems to have growing importance. Funding by the National Center for Health Services Research and other government agencies has declined, as have other funds (training grants, capitation funds) for research in universities. Access to data and to delivery settings has become a problem the university-based researcher for reasons of patient/provider confidentiality and the competitive and proprietary nature of the research information.

In this issue of *The Mount Sinai Journal* dealing with the applications of health services research to health care policy—and health care—it is relevant to consider briefly the effect of the research setting on the funding, focus, and influence of health services research. More broadly, any consumer of health care—and every such consumer is a recipient of health care policy—has a substantial interest in the impact of alternate research settings and perhaps alternate recommendations emanating from them.

This note has the modest aim of describing some of these alternate settings and comparing them with more traditional research settings along several evaluative dimensions of substance, quality, and impact. (I myself have conducted health services research in both traditional academic and nontraditional settings, including government and AHA.) I also want to raise some issues concerning the constraints (some immutable, some not) of traditional university research settings seeking to influence policy within a pluralistic society. (That is another point.)

Factors in Effectiveness

Since this note concerns the way that the varying structural constraints of a research setting influence the effectiveness of health services research, it is clearly important that I say what I mean by "effective health services research" and how I see such research either enabled or constrained from influencing health policy. I take my definition from the 1979 Institute of Medicine Working Paper (1): "Health services research is inquiring to produce knowledge about the structure, processes or effects of personal health services, the overall objective of which is to improve the provision of personal health services."

Given the latter part of this definition, "effective" health services research is research that accomplishes the goal of improving health services through a direct influence on health care policy. This direct influence sets health services research apart from most other research activities undertaken in universities, where effectiveness is measured by contribution of knowledge to a discipline and not by immediate relevance to a particular policy. This difference has profound implications for the direction of research and the professional career of the researcher.

The factors I take to be important in mediating the likelihood that a given research result will influence policy and thereby improve health care

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fall into five major categories: problem definition; study approach (descriptive vs. interventional); funding; access to data; and dissemination of results.

Traditionally these factors are seen as exclusively professional matters of technical quality reflecting only the training, experience, and quality of the researcher. Although these influences are important (2), the structural constraints imposed by a particular research setting are very significant, more so than is currently realized. I believe that for certain health service problems and/or decision-making audiences, the traditional university-based research setting may not be the one most likely to effect improvement in health services.

Traditionally, we assume that well-supported, well-trained researchers will produce research high in technical quality which, through its intrinsic appeal to reason, will influence health care. However, the impact of that research on policy is not viewed as the responsibility of the researcher or the research community, nor is its pragmatic relevance so viewed in evaluations by the academic community.

In contrast to the traditional model, a more complex one suggests that a professional or provider organization will define research issues differently, depending on the values of the organization and its possibilities to act. What comes into play are societal problem-solving values: ideology vs. "research"; activism vs. passivity; pluralism vs. monolithic health care.

These different settings have different structural constraints that affect the way a problem is identified and defined, the kind of data which will be used, and the dissemination of the research results. Further, these constraints affect the mix and quality of researchers attracted to the setting, the funding available, and the study approach. Ultimately, the structural constraints and the structural options of the research setting profoundly influence the uses of research—"ammunition," evaluation of existing program, or evidence for new intervention. More detailed discussion of the factors related to effectiveness in research is warranted before assessing variations within and between settings.

Problem Definition. A research project may be designed to test or refine a theory or to address an applied problem in the delivery of health care. Theory-oriented research will reflect the disciplinary interests of the researcher, in part determined by the researcher's perception of professional rewards (promotion, tenure) that depend on publication in refereed journals. The intended audience of this type of research is generally the peer group of the researcher. But in research which starts from some perceived dissatisfaction with a health service or an underserviced health need, the question is, whose perception of "the problem" is paramount, and how was it defined? The problem is likely to be chosen and defined by the audience of the particular research setting or the client. The setting in turn is influenced by the source of funding, institutional interests, the local interests of the community surrounding the setting, and possibly a wider community or target group defined by the institution.

Health services research implies a primary client whose interests are predominant, whether or not this predominance is recognized by the researcher. A research agenda within a setting is an exercise in client identification, with substantial consequences in problem definition. Whether researchers translate a "symptom," for instance high no-show rates for follow-up appointments, into problematic behavior by the patient or the reimbursement agent will depend on the setting in which the problem is defined.

Client identification not only implies problem definition, it raises further questions (3, 4):

Whose behavior is seen as primary to the problem and who ought to be the primary focus of intervention or study?

What is the source of this behavior and therefore the analytic target: reimbursement, provider, socialization, provider training, patient cultural norms, patient incapacity, institutional arrangements?

Which decision-making agent can best alter the source of the behavior under examination: the patient, the provider, the hospital, the state certificate of need agency, the federal Medicare agency?

What is the type of evidence, and to whom ought it be presented within the decision-making agency, to best alter the behavior? Are clinical data or descriptive case studies more effective means of inducing organizational change? Is information presented to program chiefs or to the financial audit unit?

When in the decision-making horizon will the organization have the best option for influence: at the next formal budget hearing, or during a crisis resolution after a media exposé?

These questions are clearly vital in seeking to maximize the impact of health services research on policy and program improvement. No so clear is whether most researchers (5, 6) pay sufficient attention to them; in fact, many researchers are quite unsophisticated concerning them. In brief, any research project implies particular answers and value choices, and these in turn are affected by the research setting and perceptions of the client in that setting.

Study Approach. The study approach has to do with what quality and kind of evidence are most likely to have an impact on the decision-making agency. The most scientifically rigorous evidence is by no means always the most persuasive with all agencies. The choice of descriptive vs. analytic, survey method vs. case method, and experimental, quasi-experimental, or nonexperimental design may each result in influential data. Criteria for judging the results of health service research may vary according to organizational needs. Thus, one agency may require descriptive data for a six-month period but not have time for a three-year clinical trial; another may place more emphasis on cost-effectiveness than on clinical efficiency.

There cannot be one best study approach in health services research. Study approaches will vary with the research setting, so that each will specialize in a particular methodology, whether or not that approach is likely to maximize impact on policy.

Funding. The availability of resources varies with the research setting. University-based units continue to experience both an inability to attract internal "hard" money for the support of health services research and a reduced ability to attract large-scale grants from external sources. On the other hand, research units of professional and provider organizations seem to be enjoying increased budgetary allocations from their organizations.

Funding sources often focus on certain approaches and substantive areas. Thus, both federal and private foundations tend to shy away from theoretically based analytic research and gravitate toward programatically based descriptive research and evaluation. Government contracts with precise specifications for research are replacing government grants based on the investigator's choice of subject and approach.

Access to Data. The impact and quality of a health services research project is greatly influenced by the quality of the data to which the researchers have access and the analytic relevance they can give it. The nature of the data—case histories, national surveys, self-selected samples of patients, or clinical trials of program intervention—will affect the level of credibility, generalizability, timeliness, and relevance of the findings and recommendations. Traditional university-based settings have had the least access to internal provider data and are least likely to have sufficient funding to acquire data through primary data collection or national survey data tapes. Other settings are more likely to have access to high-quality data, either because they collect it themselves (AMA or AHA) or because they generate the data in the course of service.

Dissemination of Results. Until recently, dissemination of results beyond reporting in journals to scientific peers was not seen as a necessary part of health services research. It is now seen as necessary, although it is frequently seen as an activity separate from and less important than the research itself and one that could well be completed perfunctorily by distributing a press release to local media.

For effectiveness in application, dissemination of results is an integral part of the process, starting with problem identification—which specifies the decision to be influenced, by whom it will be made, the constituencies which influence it, and the type of evidence likely to be most useful to each constituency. Thus, at the earliest stage, a strategy is developed for communication of the results and the form it should take. One hopes that each constituency to whom the results will be disseminated will have been consulted through advisory committee structures throughout the research process.

Some research settings are better positioned than others for dissemination of results by being at the hub, or at least being an integral part, of a preexisting communications network. Thus, if physician behavior is the behavior to be influenced, an AMA study is likely to be most influential. Similarly, an intramural government study is more likely to influence government policy.

Variations in Research Settings

Health services research is performed in seven settings; only two of these, both in universities, are traditional and well-known (Table). The other five are growing in importance as sources of funding, data, and production of health service research. Precisely because these settings vary from traditional ones, it is useful to describe them. In doing so, there is a danger of underestimating the effect on research of variables not related to the setting. Thus, it is not always the case that research in provider organizations is more likely than research in a university to be problem-focussed, have good data access, and be well integrated in a dissemination network. At times the influence of the researcher's discipline or preference, or the topic itself, may override the constraints of the setting. Nevertheless, research settings do have constraints and, while these may change over time, understanding them offers considerable promise for better research.

TABLE

Factors Related to Effectiveness of Health Services Research by Setting

Setting	Factor				
	Problem definition	Validity approach	Funding access	Data access	Policy influence
University					
Graduate school	Theoretic	Internal	Low	Low	Low
Applied schools	Intermediate	Internal	Medium	Low	Low
Government					
Federal provider	Practical	External	High	High	High
Federal research unit	Theoretic	External	Medium	Medium	Medium
Local	Practical	External	Medium	High	Medium
Nongovernment National					
Provider	Practical	External	High	High	High
Nonuniversity research institute	Intermediate	External	Medium	Low	Medium

University. The traditional setting for health services research is the graduate school or liberal arts faculty of universities, typically in a department, more rarely in research centers or institutes. With the decline of both internal and external funding for these units their staff has diminished. Research projects within universities are most likely to be designed to test a model and develop a theory rather than solve a practical problem. The study approach is most likely to emphasize internal validity as opposed to generalizability of results. Indeed, the relative isolation of most university graduate schools is what has placed them at a peculiar disadvantage for data access and dissemination of results. They are not associated with agencies that routinely collect data of relevance to health services research, nor is funding likely to be available for primary data collection. Similarly, graduate schools are not likely to see their responsibility for dissemination extended beyond publication of journal articles.

The other university-based setting is the school of "applied" knowledge—medicine, public health, business, management, or public administration. These are seen by funding agencies as attractive multidisciplinary units likely to be more interested than their graduate school colleagues in program-derived projects. Indeed, both the federal and private sectors have funded such units.

Government Settings. In the past, government involvement in health services research has been primarily to award grants to university-based researchers. Two factors have led to more direct involvement. The National Institutes of Health, while retaining their primary emphasis on clinical research, now support research on the impact of health services in the diagnosis and treatment of disease. This support is both intramural and through external grants. In addition, several government agencies that either provide or reimburse health services have established their own research units. These units study issues that are too political or too confidential to be entrusted to the university research community, or that universities were not able or willing to respond to in a timely manner.

Three major types of research units are government-based: federal providers, federal research agencies, and local government.

The rationale of federal provider-based research units is problem-focused research. Thus, the Veterans Administration hospital system funds both a central office and hospital-based programs to undertake research projects aimed at solving management problems, such as patient compliance or clinical and administrative information systems. Similarly, HCFA has its own research and evaluation unit. Provider-based units have, by and large, enjoyed substantial funding as well as privileged access to internal data sets. At the center of a provider network, such units are also well prepared for dissemination of results and incorporation into operational policies. The ability of these units to conduct studies of changes in program intervention is obviously greater than that of external units, which must often limit research to descriptive observation of programs in operation. Issues referred to provider research units for examination are likely to be those about which decisions are pending; timeliness is therefore insured.

The other major federal setting is a research agency, such as one of the National Institutes of Health or the National Center for Health Services Research. These units have the advantage of a sophisticated research environment staffed with full-time dedicated researchers. Units have access to large data sets, often years before it is available to the outside research community. The researcher can also develop surveys or insert survey items in routine reporting forms. The disadvantage of the federal research setting compared to those in provider agencies revolves around reduced ability to affect the operational policies of health programs.

The third type of government-based research setting is a unit attached to local (state or city) health or human resource departments. These units have emerged only in the last few years, partly in response to the growing need for centralized program evaluation, and partly as a research outgrowth of hospital regulation and rate-setting activities. They tend not to be well funded but to enjoy access to well-developed data sets and to have some influence over policy, but not over operations. At present they are policy analysis units more than research analysts.

Nongovernment Settings. The growth of nonpublic provider-based research units has been remarkable over the last 10 years. The AMA, the AHA, The Catholic Hospital Association, The Federation of American Hospitals (representing proprietory hospitals), and the Blue Cross Association of America all have extensive research and policy analysis staffs led by a director of research with a budget of at least $500,000. This growth reflects a growing need for research results to influence executive and legislative policy with respect to regulation, licensure, or reimbursement, for instance. The development or defense of health care policies in the public arena is now, more than ever before, a research-backed activity. Each side must cite credible research to support its own position and to attack the opposition. "Research" lends credibility to an argument.

These provider-based units enjoy access to restricted data sets. Furthermore, they are well funded internally and by foundation and government dollars. This support and access to data have attracted well-trained researchers who publish in traditional journals and also have an opportunity to disseminate their findings and influence policy positions within their organizations. Thus, research units in such national settings are more likely to influence policy than operations.

Of particular interest for operations are the local provider-based counterparts. Most hospital chains, many individual hospitals, many local hospital associations, Blue Cross and Blue Shield plans, and health maintenance organizations have research centers. These address issues of patient compliance, marketing, and reimbursement, and provide policy analyses and program evaluations.

Another nongovernment research setting is the unaffiliated research institute. Such units do not generally enjoy large endowments, and are therefore dependent on external funding from foundations and government agencies. The most productive of these—such as Rand and the Urban Institute—have been quite successful with grant awards. However, they have no preferred access to "in-house" data sets, nor have they any particular advantages for dissemination. As research contractors, they can claim the rigourous methodologic standards of universities and are substantially more timely than research contractors in universities. Consequently, they have played a major role in influencing government policy.

Summary. Not only are there new research settings for health services research in addition to those in the traditional university, but some of them have advantages for effectiveness. In particular, provider-based units are likely to have preferred access to "in-house" data, to be centrally placed in dissemination networks, and to enjoy a reasonably high level of funding.

These developments have implications for research funding, for employment of researchers, and for data access at a time when university settings are suffering from a decline in resources. These new settings are consequently more effective in maximizing the impact of health services research on health care policy and programs.

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Seminars for Congressional Aides: An Educational Program on the Role of the Urban Academic Medical Center

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Congressional health legislative aides have a significant impact on developing federal legislative policy in respect to academic medical centers and the issues surrounding those centers. Such issues include capital reimbursement, graduate medical education, biomedical research, technology advances and impact on care, unreimbursed care, manpower requirements, and cost containment measures. However, as a previous study in this journal indicated, such staff members are young, experience high turnover rates, are responsible for numerous issues in addition to health, are stressed for time, and are pressured by rapidly moving situations. Only 2% have been trained in the health professions. The Mount Sinai Medical Center Auxiliary Board organized two programs of visits to Mount Sinai in 1982 and 1983; a total of 16 of the key health legislative aides attended. This article explains the reasons for the visits, construction of the agenda, and results. It is hoped that other academic medical centers will consider this a useful model for the development of similar programs.

In 1982 and 1983 the Legislative Committee of the Auxiliary Board, The Mount Sinai Medical Center, sponsored what promises to become a series of seminars for Congressional health legislative aides and other federal government officials. The seminars focused on the role of the urban, academic medical center in the national health care system. They were sparked by the Legislative Committee's growing awareness of the key role such staff members play in setting Washington's agenda for health care issues that have a powerful impact on academic medical centers. As the Legislative Committee came to understand the limited exposure of many Congressional staff to institutions like Mount Sinai, it became apparent that action was needed to increase their understanding of what an academic medical center is and does.

The Auxiliary Board's Legislative Committee sponsors an educational program devoted to informing themselves and Mount Sinai staff about the impact of public policy on patient care and the viability and stability of academic medical centers. The committee's volunteer membership is independent of medical center administration, thus differing from a professional staff group or a board of trustees, both of which would be concerned primarily with the individual institution's needs.

In December 1981, the Legislative Committee invited a single Congressional health legislative aide to Mount Sinai. The goal was to become informed about the political decision-making process and current health care issues at the federal level. A tour of patient care areas and a follow-up discussion were arranged.

This initial experience clearly demonstrated that all parties would gain from more knowledge about each other's concerns. Concurrently, Dr. Grupenhoff's research ("Profile of Congressional

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Health Legislative Aides," published in *The Mount Sinai Journal of Medicine* in January 1983) indicated that turnover among Congressional health staff was frequent. It also revealed that many of them were young and burdened with numerous areas of responsibility in addition to health policy. Only 2% had training in the health professions. It appeared that a broad and comprehensive educational experience with an academic medical center could be especially useful to these aides.

The Committee also determined that, in addition to Congressional aides, other individuals involved in national health care issues, such as professional staff to Congressional health committees, and researchers and policy-makers from other Congressional support agencies, should be included. It was felt that a meaningful program for those with many years of experience as well as for younger staff members and aides could be developed.

Planning. Long before the first program took place, a lengthy and detailed planning process was undertaken. Among the participants were Thomas C. Chalmers, M.D., who was then president of the medical center and dean of the Mount Sinai School of Medicine; other faculty members of the medical school; Alfred R. Stern, chairman of Mount Sinai's board of trustees at that time; Dr. Grupenhoff; and members of the Auxiliary Board. Advice and comments were sought also from such groups as the Association of American Medical Colleges, since the goal was to discuss academic medical centers generically, rather than to focus only on Mount Sinai.

This collegial process brought to light and clarified the public policy issues of greatest concern. It served also to identify the best structure and content to illustrate the academic medical center's three-fold mission of patient care, research and education.

The Legislative Committee coordinated the planning process as well as the implementation of the project. Their sponsorship proved to be a boon for several reasons beyond the obvious one of their interest in and willingness to bring the idea to fruition. It strengthened the credibility of the generic, nonpolitical approach; and the Auxiliary Board's ability to underwrite the expense of the seminars from philanthropic funds prevented conflict of interest questions from being raised. If institutional funds had been used, many of those who were invited would have felt that it would be improper to accept payment of travel expenses, for example.

Content and Format. It was agreed that the topics to be addressed should be broad-based, covering such issues as:

- how an academic medical center differs from a community hospital
- the impact of federal health care policies on academic medical centers
- whether the high cost of health care in an academic medical center is justified
- whether the "physician glut" is myth or reality
- the capital financing needs of an urban medical center with an antiquated physical plant
- the academic medical center's view of regionalization and sharing of resources with other medical institutions
- the medical school's responsibility to train future physicians in cost containment

It was also decided that the lecture hall approach would be unsuitable and fail to achieve the goal of illustrating the many activities that occur in a medical center on a typical day. Instead, short talks by key faculty members would be followed by a tour designed to point up the interrelationship of teaching, research and patient care. Discussion and follow-up questions would take place during an informal lunch. Briefing material would be provided so that attendees could prepare in advance.

Attendance. Sixteen people have attended the two seminars held to date. About half were from Congressional offices, and about half from committee staffs. A staff member of the Congressional Budget Office who prepares cost estimates and impact estimates for the Congress on specific amendments also attended, as did the director of the health staff of the Congressional Research Service of the Library of Congress, which prepares briefing papers for Congress and its committees.

Implementation. A personal invitation to the seminar was followed by a letter from the Auxiliary Board and Dr. Chalmers, with more details on the day's activities. The date of the seminar was chosen to be a Friday of a week in which Congress was in session, because the most intense Congressional activity occurs from Tuesday through Thursday. It was decided not to hold the seminar during Congressional recesses since these are times when many potential attendees schedule vacations.

The letter was followed by a personal visit to each prospective participant. At that time the kit of materials prepared by the Legislative Committee and the medical center's Department of Public Affairs was delivered. The kit included an agenda, brief information about the medical center and the Auxiliary Board, and biographies on Mount Sinai participants.

A briefing meeting was held at Mount Sinai for the seminar's faculty. This allowed each presenter to raise questions and clarify the purpose of the day and the material to be covered. It also provided an opportunity for them to become informed about the special interests and backgrounds of the legislative aides who had been invited.

On the day of the seminar, a Mount Sinai representative traveled with the group from Washington to New York and back. Approximately 70 percent of those who accepted the invitation actually attended; the remainder were detained by last-minute developments related to their work.

The concept of the one-day trip is important, not only to keep costs down, but because it is unlikely that such busy people would be able to leave their jobs for more than a day. It also became clear that the day must be structured so that the group could return to Washington by early evening.

Briefing kits were distributed once again during the trip from Washington to New York. Some used this time to read the background material; others spent the one-hour trip getting acquainted with each other. Surprisingly, many of the staffers had never had the opportunity to meet—their individual assignments are so demanding that there is little chance for interchange, although it would often be useful. An unexpected benefit of the Mount Sinai seminars was the opportunity to establish relationships with colleagues.

Upon arrival, a background briefing on the role of an academic medical center was held, followed by a discussion of the impact of federal health care policies on such institutions, and a description of the tour. The tour itself lasted two hours and included a visit to basic research laboratories and patient care areas such as the Emergency Room. It also featured what turned out to be the high point of the day: attendance at medical teaching rounds with faculty members, medical students, and house staff in which a patient was presented and discussed.

At lunch, participants had an opportunity to discuss their concerns informally. A question-and-answer period followed. Finally, closing remarks were delivered on the impact of public policy on academic medical centers. At 4 P.M. the group departed for the airport and their return flight to Washington.

Restructuring. Much was learned from this first effort, both through conversations and requests for information on the day of the seminar and in follow-up discussions with attendees. The second seminar, held in June 1983, was restructured to reflect these findings.

The formal program was shortened, and more time was allowed for dialogue.

Several components were added to the advance briefing kits, including a map of Manhattan showing Mount Sinai's location in relation to other well-known New York City landmarks. Staffers unfamiliar with the city had requested this so they could better orient themselves to the immediate communities the medical center serves. More data were provided regarding the medical center's sources of income, patients served and patient mix, number of research projects and scientific papers published, and number and mix of graduate and undergraduate students. A written statement on the role of the academic medical center was also added.

The introductory briefing was kept short, and the morning's agenda focused on attendance at teaching rounds. Once again, this proved to be the day's most popular activity. Of the 16 people who attended the two seminars, only three were physicians. They were the only participants who had ever had the opportunity to attend medical rounds previously. For the first time, many staffers saw for themselves how patient care, research and teaching are intertwined. This sense of integration was particularly impressive, and the visitors expressed amazement at the degree to which the department chairman involved was aware of the individual patient's problem, and how it related to research taking place both at Mount Sinai and around the country. The result was a graphic illustration of the relationship between the National Institutes of Health and academic medical centers. Attendees also learned at first hand that much of medical education is a one-on-one process, and that often residents and faculty are spurred on by students' questioning.

The theme of the afternoon session was closely related to a topic of great concern to all: managing an urban teaching hospital in an era of cost containment and finite resources.

Questions Raised. At both seminars, attendees raised many significant questions during the couse of the day, indicating the wide-ranging interests and concerns of this group, as well as the areas in which academic medical centers have an obligation to inform legislative aides. The topics raised included:

- What populations are served by urban academic medical centers?
- How do such institutions serve their communities, and how do they differ from community hospitals?
- Why should a tertiary care center also provide primary and secondary care?
- How does Mount Sinai justify the highly specialized and expensive care provided to some patients when there is a medically underserved community at its doorstep?
- How are academic medical centers teaching students to be more conscious of their role in controlling the cost of medical care?
- How much should society spend on advanced technology and research?
- What are the advantages of conducting basic research at an academic medical center rather than at a university?
- Who should be given priority for medical care?
- Who has the responsibility to determine who should live and who should die?

Evaluation. Following each seminar, written comments were requested from participants, who also received letters from the president of the Auxiliary Board thanking them for attending. In general, reaction was highly favorable, and most aides singled out the teaching rounds as the most impressive and profitable part of the day. Requests for more unstructured question and discussion time, and for a longer and more detailed presentation on the financing of an academic medical center were taken into account in planning the second seminar. A discussion of the role of basic research, which some found difficult to follow, was dropped from the program after the first seminar. The tour was also redesigned to focus exclusively on rounds, reflecting comments that it was confusing and time-consuming to visit several different areas of the medical center. As previously noted, information was added to the briefing materials to further respond to requests and comments.

Conclusion. Despite the many pressures of their jobs, Congressional aides with responsibility for health care issues are well-informed, dedicated and intelligent people. They welcome the opportunity to learn more about the complex problems of academic medical centers. Efforts to communicate with this group are well-received and have led to further opportunities for contact and discussion. In the current climate of budget-cutting and cost containment, it is particularly important for institutions like Mount Sinai to have an open channel of communication to those who advise members of Congress on health care legislation. The seminars provided a vehicle for establishing such channels, and continuing contact is maintained by members of Mount Sinai's faculty and administration, and by Auxiliary Board Legislative Committee members. The results have been useful and gratifying.

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The Role of Research When a Biomedical Issue Is Politicized: the Regulation of Methadone Maintenance Programs

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Over the past two decades heroin dependency and approaches to its therapy have occupied the public limelight as America's major drug problem. Attempts to ameliorate the problem of heroin dependency have revolved primarily around policies aimed first at decreasing the supply of the drug by curbing the growth of opium poppy abroad (1) and by reducing its influx across the border, and second at decreasing demand through education and therapeutic interventions, in particular methadone maintenance.

Despite all international and local efforts to limit supply, in the period 1980–1984 poppy crops increased 50% (2) and the importation of the converted heroin has not abated.

The economic impact of this heroin trade is manifold. The cost of heroin dependency in the United States is estimated as in excess of $3.5 billion, including both the cost of the drug to the user and the cost to federal, state, and city governments for personnel and other expenditures on institutions for confinement (3). The dependent individual often engages in crime (burglaries, muggings, prostitution) to support a habit which frequently exceeds $100 a day. The victims of these crimes may suffer financial losses not included in the above estimate. Furthermore, to the extent that the addict is unable to remain gainfully employed and requires public relief, society bears additional direct and indirect costs.

Because of the social and medical implications of heroin abuse, the solution to it requires a multidimensional approach, and has attracted the attention of policy makers within government and researchers in the biomedical community. However, as a result of the politicization of heroin dependency, significant barriers have been raised to the implementation of public policy based on research data.

Decreasing the Demand for Heroin. Strategies for decreasing the demand for heroin have included drug education, rehabilitation centers and therapeutic communities for drug abusers, and methadone therapy and maintenance programs.

Drug education, in particular for the young and susceptible, is viewed as having a large potential role in decreasing drug use. However, a recent Rand Corporation study on American drug control strategies concludes that although prevention programs are promising, some education programs have had "conflicting, ambiguous or zero effects" (2, 4).

Therapeutic communities and rehabilitation centers have emphasized the return to a drug-free state through the process of education, counseling, and self-discovery. The effectiveness of this approach has been variable, some programs reporting significant improvement of their members and others reporting failures (3). In addition, this form of therapeutic intervention is often not acceptable to addicts, limiting its usefulness.

In 1964 clinical research into the use of methadone for long-term treatment of "hard-core" heroin abusers was initiated by Drs. Vincent Dole and Marie Nyswander in New York City (5). This pioneering research demonstrated that metha-

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done could prevent the drug-hunger and drug-seeking behavior of the heroin addict through the development of a stable tolerance threshold to narcotics. The methadone-maintained individual was shown to have a high tolerance threshold produced by methadone, which blunted the euphorogenic action of heroin and eliminated the acute withdrawal syndrome. It was felt that by keeping patients free of withdrawal symptoms, the process of social rehabilitation could be carried out. Subsequent methadone maintenance studies reported marked reduction of illicit drug use among participants, decrease in criminal activity, and improvement of productive life (3).

By the late 1960s the use of heroin had reached epidemic dimensions, particularly in large urban areas. In response, the use of methadone spread rapidly. However, along with the apparent benefits of methadone therapy, there were problems stemming from its increased availability, difficulties associated with the management of large numbers of addicted patients in hospitals and clinics, growing opposition to maintenance by drug-freedom advocates and communities reluctant to house maintenance programs. As a result of these and other developments, in the early 1970s federal and local governments established regulations and guidelines on patient enrollment, maintenance dosage protocols, and managerial standards (for example, the Comprehensive Drug Prevention and Control Act of 1970). These developments in the biomedical, social, and public policy arenas were often fraught with controversies and bitter conflicts of interest.

Methadone Maintenance: Research and Public Policy

The vast majority of research into heroin dependency and methadone treatment over the past two decades can be broadly categorized as concerned with either the biomedical effects of addiction and maintenance (tolerance, medical complications, dosing) or with the social and economic impact of drug and therapy (crime reduction, job rehabilitation, family integrity, epidemiology of users). The impetus for this work has been variable. Often research is carried out by individuals whose stated goals are to improve understanding of the clinical and social implications of dependency and therapy, to gain insight into the biochemical basis of the actions and responses to a given drug, to review the psychosocial significance of the dependent state and maintenance, or to devise methods of decreasing the morbidity and mortality of the addict. Seldom is this research action oriented. Most of it is not specifically aimed at introducing policies for drug treatment or at shaping or altering existing policies.

The researcher's underlying aim is frequently that of contributing to an area of scientific interest with work that is at the cutting edge of the field. The reward for good work may be recognition in the biomedical community and advancement up the academic ladder. Also, to the extent that research materials and salary support are derived from grant funds, the researcher attempts to be "productive" in order to gain future access to research funds.

The constraints placed on the researcher's work are usually those imposed by funding sources (predetermined by grant proposals that define the scope and depth of the proposed study), journal criteria for publication, regulations of institutions of employment, and professional standards and ethics.

Whenever such incentives and constraints are operative, the researcher is not likely to emphasize the nonbiomedical aspects or policy implications of a project. These are viewed as being within the purview of politicians, program administrators, or other decision makers. For instance, even though the medical effects of heroin dependency and methadone maintenance are well described and their social impact understood as a result of many research studies, seldom have these investigations addressed the issue of improving or changing regulations, or making policy decisions more responsive to the needs of patients and persons unable to receive treatment. Researchers may not be aware of or may not even be interested in applicability to decision making and significant change.

The policy makers, like the researchers, have multiple goals. Among these they list the development, institution, and support of programs which are effective, economical, and acceptable. They are interested in the impact of drug-abuse programs on their target populations and in the economic and political costs of program implementation. Because of the controversies over heroin abuse and methadone maintenance, a key goal is that of containing the political cost of program creation or expansion.

Policy makers are constrained by the political climate in which they operate. They have to contend with vocal community groups who, although claiming support for programs to treat the drug dependent, adamantly oppose the creation of any such program in their neighborhoods. These groups would rather live with the invisible social costs of addiction than with the visible reality of addicts leaving and entering a local methadone maintenance program. In addition, the policy maker must deal with health care providers and well-organized pressure groups (such as the drug-freedom advocates) who oppose methadone maintenance and have political clout and access to the media. Finally, many decision makers fear that increased support for these programs may resurrect old claims of genocide perpetrated against the poor and minority groups which they mainly serve.

The issue of political constraints facing the policy maker is particularly important. The population served by methadone maintenance programs—approximately 82,000 in the U.S. (6) and 32,000 in New York State in 1984 (7)—is largely disenfranchised and without political backing. Also, program supporters are not vocal in their views and are unable or unwilling to organize for effective political action. Those patients who are doing well on methadone maintenance and might be able to influence policy (media personalities, politicians) are often reluctant to speak up because of the persisting social stigma of being on methadone. As a result of this lack of countervailing pressure, the decision maker often succombs to what appears to be pragmatic and ignores the benefits of maintenance in favor of preserving current levels of services or reducing, defunding, or further regulating existing programs.

In discussing the impact of social research on policies for detoxification centers in Ontario, Ogborne and Smart noted that "some researchers have seen their best efforts completely ignored, while others have witnessed sound research results debunked or distorted for political ends. Rarely, it seems does research have the kinds of impact that its authors had hoped" (8). This observation is also widely applicable to the United States, where some policy makers admit that most research into heroin abuse and methadone maintenance is either viewed with skepticism or simply ignored.

Policy makers and their delegates often do not have sufficient background in the biomedical sciences to understand and interpret research findings. As a result, many well-designed studies go unnoticed. On the other hand, when studies and their implications are understood, they may be of little practical interest. For instance, a decision maker may be interested in results concerned with methadone dosages and length of treatment, and will evaluate findings in these areas carefully. These studies may impact on federal or state regulations for dosing and treatment lengths. However, research results pertinent to issues not currently under consideration or which support politically unpopular alternatives to the status quo—on expansion of maintenance programs for example—may have little or no impact on policy. The decision maker is not likely to risk the political repercussions which may result from a change of policy direction.

Some researchers have complained that existing regulations defining how methadone therapy must be provided are not supported by any research and are often contrary to empirical evidence (9). This realization is disenchanting to many investigators who feel that policy makers have demonstrated little interest in facts, upon which regulations and policy should be based.

Even when research is carried out with the support or under the auspices of government, action based on research findings is often lacking. For example, a recent publication from the Department of Health and Human Services entitled "Research on the Treatment of Narcotic Addiction" concludes that much of the criticism against methadone clinics is contrary to scientifically generated data. In addition, it notes that while patients remain in treatment, criminal behavior and illicit opiate use is reduced, employment increases, and the general health of chronic methadone users improves. Finally, the report suggests that the drug has no major adverse consequence with prolonged use, and that attempts to limit the dose or duration of treatment are therapeutically unjustified (10). Despite these findings, published by the Department of Health, no serious attempt has been made to provide methadone to all the heroin abusers who request treatment—many methadone clinics report long waiting lists (11)—let alone those individuals who would benefit from maintenance but have not sought services. Moreover, many methadone programs are being asked to reduce costs, even though costs have not increased over the past decade. This results in a weaker rehabilitation effort and less favorable outcomes, thereby fueling criticisms that methadone therapy is not effective. Policy makers find themselves responding to political and social pressures—their "realities"—not necessarily to research results.

What Can Be Done?

On the issue of heroin dependency and methadone maintenance, there tends to be a wide gap between researchers and policy makers. The highly politicized controversies over drug abuse and its treatment tend to divide not only researchers and decision makers, but also health care providers, who often have differences with respect to modes of therapy. However, some steps can be taken to narrow the gap.

Spell Out Policy Implications. First, the serious researcher undertaking a project with implications for patient care or improvement of services should not be discouraged by the prospect of lack of action on findings. Rather, researchers should attempt to make the research relevant to the policy maker by spelling out the policy implications of results and the potential costs and benefits associated with alternative options. The researcher also has a responsibility to be articulate about research findings and supply information not only to policy makers, but also to the media and to persons or groups that may create pressure for action.

Contracts between researchers and decision makers that spell out exactly how research results should be utilized have been suggested by some authors (8). However, such an approach is currently untenable, given the structure of substance abuse regulatory agencies; the decision maker often does not directly evaluate research findings. In addition, the decision maker must contend with a political climate which favors even further regulations and reduction in services, despite research evidence suggesting the contrary.

Discover Goals and Constraints. Second, researchers should urge policy makers to make their goals and constraints for action known to the researcher. This may commit the decision maker to a certain path and allow the researcher to develop strategies for projects which can impact on policy matters. Vague or very broad goals serve only to justify poor performance. Therefore, every attempt should be made to obtain a clear and specific outline of the plans of the decision makers and the client agency.

Become a Political Voice. Third, drug abuse and methadone maintenance programs are politically sensitive issues, and decision makers in government are expected to act in accordance with the views of their constituencies. To the extent that this premise holds, it behooves researchers and providers to make their views on these issues known to their government officials. They could have a significant impact on policy if they were organized. Their opinions on addiction and therapy would have more weight. The popular media can also be used to inform public opinion of the well-substantiated social and medical benefits associated with methadone maintenance. Actions such as these may impact upon policy to a larger extent than the best designed research projects.

Seek Representation on Regulatory Agencies. Fourth, state and federal drug abuse regulatory agencies should seek a wider and more active representation of researchers and providers in their goal setting and project evaluation efforts. This would serve to develop a context for the application of research findings, and to establish a common ground upon which the impact and success of government sponsored programs can be judged.

Emphasize Human Services. Finally, it is the welfare of the heroin-dependent person that is ultimately at stake. These are the people most affected by the discordance between research findings and policy setting. The efforts and sights of both researchers and policy makers should be aimed at helping and treating this addicted population, de-emphasizing personal advancement or political repercussions.

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Can Academic Medical Center Health Services Research Be Useful in Community Development?

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Medical schools continue to place emphasis on medical specialization and biomedical research, but they devote little attention to health services research (1). Many educators believe that if medical schools are to maintain their primary function in the transfer of knowledge and in the creation of new knowledge, their role should include help to develop demonstration models of service as well as to study these models from the standpoint of medical care use, costs, manpower requirements, and new uses of manpower (2).

This paper describes how the Department of Community Medicine of the Mount Sinai School of Medicine moves outside its institutional walls as it utilizes research findings to help community decision makers plan and develop health care models and research projects designed to meet community needs. The reciprocal tasks which researchers and decision makers perform as they develop their projects are identified and discussed.

The Department as a Research Resource. The Mount Sinai School of Medicine has from the beginning mandated the Department of Community Medicine to serve as a bridge between the resources in the medical center and in the surrounding community of East Harlem (3). The department's approach to community groups, whether community or provider organizations, embodies the principle of "doing with" rather than "doing for."

The department's generic style entails encouraging and stimulating community requests for assistance in health planning, development and evaluation. The department then implements this help by participating, collaborating, and consulting with local groups, using the technical resources and expertise of its faculty (4).

An early concern of the department was to learn how the medical center could assist in improving health in East Harlem, an underserved Manhattan community lying north of 96th Street and east of Fifth Avenue and abutting the medical center. Understanding the community's needs and resources was the first major research task of the department, which had two initial goals: to establish a solid demographic and health data base about the community and to make existing community groups of consumers and providers aware that an academic resource interested in the application of health research findings was available.

We soon saw that we needed an unbiased assessment of the community's status, resources, and problems, against which to assess a possible potpourri of requests based on the priorities of special-interest groups. A household survey was undertaken. All plans were reviewed with representatives of the community, who also helped researchers prepare a Spanish version of the questionnaire. Following a pretest, 2% stratified probability sample of households was selected. Interviews were completed with 78% of the respondents from the sample.

Because the survey was carried out in 1970, the data could be compared with that year's U.S. census data. Through the census, we obtained demographic characteristics of the East Harlem

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population. For example, 80% were minority households, Puerto Rican and black. Many households had no income from employment; most of those who worked held low-paying jobs.

The department's survey showed that the incidence of social problems and the level of morbidity were high. The survey identified a common set of problems among ethnic groups. Health care needs were high on their list of priorities.

Striking data detailed where East Harlem residents went for their health services. Almost half of all outpatient visits by area residents were to facilities outside the community; 60% of these were to hospital and free-standing clinics, 40% to private physicians. The main deficit in health services was in primary care and comprehensive health services. Rates of emergency room use were high, suggesting lack of continuity of care. The survey revealed that many community organizations were working to improve the quality of community life. There was also considerable evidence that these efforts had been productive and were likely to continue so (5).

The survey findings were reviewed with different groups in the community over the next year, culminating in the publication of a monograph (6). The findings were shared with local organizations when they became available and were used in their efforts to obtain project funding.

The department updates the survey by adding relevant information about the community as it is reported by researchers and public or private agencies. In 1980, coinciding with that year's national census, a selected set of data was published as a handbook (7). This document also was shared with local groups for their use in program development. Making available important base information for application to specific community problems is a method the department uses to promote the development of community medicine and community health services.

Application of Research to Programs. For community groups to perceive research data as relevant and valuable to their needs, they need to experience the application first hand. It is necessary also to study separately how the community is helped to apply these research findings so the process can be characterized. Such study required a thorough understanding of the community and its structure. Between 1970 and 1973, a series of activities, such as screening child health in schools and training community health workers, were carried out by the department with a variety of community groups. These activities (8, 9) helped us appreciate the gap between the "ivory tower" and the "store-front" agency and to define the operational approach to closing the gap in order to improve health care in the area. We learned that preformed solutions are ineffective; that a study of needs is a prerequisite to developing solutions; that training community leaders is essential; and that the department had to be prepared to make long-term commitments to the community's agencies.

The policy finally established was inspired by the participatory land-grant college model (10), which the department adapted to academic cooperation with inner-city community agencies, particularly in regard to planning more effective organization of local health-care services. With this policy as a basis, the service goals and objectives of the department were agreed upon, and a cooperative research and development model was put into action (11). Since 1975, departmental faculty members have used the model in partnership with a number of community groups whose leaders have learned how to systematically apply research findings in making their own policy decisions in their own health programs; community groups and medical school faculty engage in a staged process of reciprocal tasks which integrate services with research and evaluation (Table). Our representative work with one community group illustrates the application of the model.

Case Study

Step 1: Study. In 1973 the East Harlem Council for Human Services (EHCHS), a Puerto Rican community organization then particularly involved in housing development, became aware of both the morbidity and mortality of area residents and of the access barriers to the four major hospital providers in the community. They were concerned as well about the lack of continuity in health care in the area. They approached the department for information and advice. Two faculty members assisted them in the interpretation of data from the community survey, in the analysis of other published reports and existing data, and in the study of alternative models of health care services that might by developed and operated by a community agency (12). This exploratory, educational process helped the community group arrive at a more sophisticated assessment of the perceived problem, one which embraced the more subtle and complex factors operating in the unrelated health services. This deepened assessment put them in a better position to reassess their strengths and weaknesses and to study alternative solutions.

TABLE

	Community group (decision makers)	Medical school (faculty advisors)
Step 1.	Becomes aware of health problems and health services needs. ↓	Studies health ←problems and needs; provides information, assists in setting priorities.
Step 2.	Decides to solve, by itself, its health problems. Chooses a model. ↓	Advises on type of ←services needed and alternative models of health care.
Step 3.	Designs and plans a program. Writes proposals for organizing health care program. ↓	Consults in design and ←program planning. Assists in defining program goals, scope of services, methods, and in writing grant proposals.
Step 4.	Organizes and provides services. ↓	Assists in organization ←and management implementation.
Step 5.	Needs evaluation and research to make decisions. ↓	Evaluation and ←research assistance.
Step 6.	Uses research and evaluation findings to make decisions that improve services.	Presents and analyzes ←research and evaluation findings.

Step 2: Choosing a Model. The department had been providing research and development assistance since 1970 to the New York City Department of Health for the development of a nurse practitioner-run child health station (13). We shared research data from that model with the East Harlem Council for Human Services (EHCHS). They decided to emulate that model, but expand it to serve adults, incorporating similar staffing patterns, clinical protocols, and outreach component deploying community health workers.

In this process the community leaders learned the principles of how to select a program model and how to build on existing models.

Step 3: Designing the Program. In July 1974, we assisted the EHCHS to develop a grant proposal that was funded six months later by the federal government (14).

In this phase, the community group acquired increasingly sophisticated knowledge of the multiple steps involved in designing a program. This experience helped them to integrate such knowledge as they applied it to the preparation of a funding proposal. Further, they learned to negotiate with granting agencies.

Step 4: Organizing and Implementing. When the EHCHS and the department reviewed the evaluation data for the Health Department model, the East Harlem group proposed taking over this child health station from the City Health Department. Early in 1975, with funding assured from HEW the New York City Health Department and the EHCHS agreed that EHCHS would operate a neighborhood health center using the practitioner model in the same facility in which the child health demonstration had been. The scope of services would be expanded and the target population would be patients of all ages.

Steps 5 and 6: Evaluation and Development. During its second year of operation, the governing board of EHCHS specifically requested technical assistance from the department faculty to learn (a) how to use data from the health center's operation, such as monthly statistical reports; (b) how to identify utilization and productivity trends; (c) how to use data reports to decide among alternative technical recommendations made by the center's staff; and (d) how to analyze expenditures in relation to the health needs of the community and the health center's objectives and sources of income. During a one-year period, departmental faculty concentrated on helping the program's leaders with a special training program for members of the board (15).

The clear interaction between evaluation, research, and decision making continued to be evident in the EHCHS center.

During the fifth year of operation, the center's executive staff asked the department to help them evaluate provider productivity, which they thought was low, and to identify related factors. Joint evaluation by the agency and the DCM faculty member pinpointed a provider productivity below federal standards. This had serious impact on the center's revenues. The subsequent identification of factors influencing provider productivity were useful in improvements.

In 1980 the management of the center noted they lacked information to address marketing needs. A patient-origin study was conducted jointly by the department and center staff. A sample was drawn from active users, and from patient charts. Residences were clustered by census tracts. Penetration rates by census tract enabled marketing strategies to be reoriented and the service area of the center to be redefined. Patient-origin surveys are now conducted every two years.

In 1983, the health center staff asked for assistance in evaluating its prenatal program. A review of 130 medical charts of prenatal patients revealed: (a) lack of appropriate health education; (b) poor referral procedures to the hospital for delivery and from the hospital to the center for postpartum care; (c) a high number of deliveries with low birth weight; and (d) the need for refined criteria for identifying high-risk patients. At the beginning of 1984, a proposal was funded to study prevention of low birth weight and to correct other prenatal program deficiencies. Currently this new program is in its implementation phase. Its services are comprehensive, including health education and social services.

Center executives have repeatedly discussed with us the center's need for alternative forms of more efficient reimbursement. A private foundation funded a proposal we prepared jointly to plan, develop, and implement a prepaid services demonstration project for Medicaid-eligible persons. Over a period of eighteen months, center staff, with assistance from department consultants, completed the first two stages of the project. Analysis of Medicaid utilization, cost data, and marketing studies were undertaken to prepare a plan to implement a prepaid delivery model designed by the agency. Federal and state regulations at that time did not allow the agency to proceed with implementation (16). However, data gathered during the development phase has been used to improve the center's operating efficiency.

Over the years of the center's operation, its leaders have acquired considerable technical knowledge of health care planning, delivery, and evaluation. This gradual, incremental acquisition of sophisticated knowledge illustrates the ongoing development of the community group. It points up the steps and processes essential for this transfer of knowledge to take place, and it illustrates how a medical school can meet the research needs of consumers at different stages of their development.

Discussion

The strategy behind all of the department's research and development efforts during its first decade and a half was to establish credibility in the community and to assist in the development of grassroots community programs. Through transfer of knowledge and skills and the type of research and development activities described here, the department has had an impact on health care delivery in its immediate geographic area. It has participated in the design and reformulation of many different public and private health care models which are becoming components of an organized system in its surrounding community. The EHCHS program analyzed in this paper is only one example of a primary care component developed by the private sector. Fostered by the department, formal linkages between different components of the health care delivery system in the area have been established. Mount Sinai's own teaching hospital is increasing links to other programs performing the role of secondary and/or tertiary care component for the East Harlem system. The growing interaction between the different components of the system is likely to improve continuity of health care, serve as a base for the future conduct of relevant research in the area, and further the application and dissemination of results.

Many categorical research projects have been undertaken in this same geographic area since the department was established. These research projects were always planned in the light of health care needs and priorities identified jointly with the community. They have included studies of adolescent health problems with special concentration on sex education and drug abuse; nutrition; health career development; vision screening with an electronic refraction instrument; studies on drinking behavior; patient compliance with medical-technological innovation; and the evalution of new communications techniques in the delivery of health care.

In general, our research and development activities in a geographically defined neighborhood bring out in the open many of the unanswered questions and issues that are at the heart of current public policy debate in the nation. Further research therefore can be expected to generate new and applied knowledge and experience that may point the direction for needed change in the national health care scene. The intention of the Department of Community Medicine is to evolve toward an ongoing health services research program which, while based in the medical center, continues to be responsive to the immediate health problems of the community in which it is located and to which it relates. The activities of the department will be evaluated in the long run in terms of its approach to health planning, its achievements in research and in the translation of research findings to the rational use of resources in the surrounding community.

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Arbitrating Change in Staff Attitudes and Training Programs on a Surgical Service

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A pilot study was conducted on the Surgical Service of the Millard Fillmore Hospital from July 1983 through June 1984 with the immediate goal of devising a format allowing open communication between surgical residents, the attending surgeons, and the program director. The ultimate goal was to develop a consensus among residents and attendings on the resident training program.

This paper focuses on the technique developed during the study by the program director and the ethnologist who participated in the study. The technique consists of three successive phases:

- individual interviews with all members of the service
- discussions in small groups on topics suggested by individual interviews
- reporting results of the negotiated conclusions of the small groups to the entire service for open discussion and final conclusions.

Methods

The study was conducted on the Surgical Service of the Millard Fillmore Hospital from July 1983 through June 1984. Participating in the study were residents, attending surgeons, the program director, and an ethnologist as study facilitator.

The study comprised three successive phases: individual interviews; small-group discussions on topics suggested by individual interviews; and report of the results of the negotiated conclusions of the small groups to the entire service for open discussion and final conclusions.

Each phase included two parts: first, elicitation of information by the ethnologist through direct contact with members of the service, and second, collation and return of the information to all staff for verification of accuracy. The first phase began after an announcement of the forthcoming study had been sent by the program director to the entire staff of the surgical service with a request for their cooperation.

Phase 1: Individual Interviews. Three individual interviews were conducted by the ethnologist.

The first interview (10–15 min) was informative and established rapport. The project was explained and the interviewee was encouraged to ask questions. A tape recording was made to allow the interviewee to get used to talking in front of a microphone.

The second interview (approximately 20 min) started with a request that the interviewee talk freely about how he or she views himself or herself in the work environment. The ethnologist became an interested listener and did not direct the interview. This session was taperecorded and later transcribed.

The third interview was directive. The transcript of the second session was given to the interviewee, who was asked to review the text for accuracy, to categorize the information, and return it to the ethnologist, either immediately or at the interviewee's leisure. Most interviewees chose the latter. The annotated transcripts were reviewed by the ethnologist to identify common themes listed by the interviewees. Persons with

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similar themes were grouped together for small-group discussions.

Phase 2: Discussions in Small Groups. The ethnologist and the program director chose topics to be discussed from the themes and items gleaned from the individual interviews and both acted as facilitation. To encourage free discussion, the ethnologist-researcher introduced the topics and presented them in a nonbiased, objective fashion, and the program director participated only when questioned, for clarification, to summarize each issue, and to test accuracy and group opinion.

The taperecorded transcript of each discussion was circulated to each member of the group for accuracy and comments. Transcripts from each session were then reviewed by the researcher, and the information collated. Based on this information, topics for general discussion were identified and conclusions drawn by the researcher and program director.

Phase 3: General Discussion. A meeting of the entire surgical service was scheduled. The program director presented the results of phases 1 and 2. The conclusions drawn were tested for accuracy and group opinion. A consensus opinion was negotiated and established. A taperecording of this general discussion was transcribed and distributed to all members of the service to test accuracy and opinion. Comments were reviewed. A final paper was produced, stating the negotiated conclusions and plan for future action.

Results

Initially, the participants were guarded. They felt the aim of the study was to evaluate them as residents, not to improve the program by their direct input. Only after the first small-group meeting did the residents understand and trust the stated goal. Their attitude toward the researcher changed. They began calling her by her first name and stopped by to comment on the study.

Some residents did not participate because of out-of-hospital assignments, heavy service responsibilities, or personal choice. One resident dropped out of the study after the second interview because he became threatened.

Individual Interviews. Resident compliance was variable, mostly because of service commitments. At times, residents were obstinate or passive-aggressive. All participants expressed their own opinion during the unstructured interview in phase 2. However, there was fear of retaliation. Although the researcher had established rapport, during the preliminary interview some participants continued to manifest subliminal distrust. These participants did not believe they were being given an opportunity to have a say in the way the program was designed and run.

Among the surgical trainees three underlying themes were identified: personal concerns; interpersonal relationships in the work place; and the work scene.

Personal concerns were of three kinds: perception and presentation of self; how their private life was affected by their work, and vice versa; feelings connected with the pressure of their lives as surgical residents.

Interpersonal relationships at work: The residents mostly discussed interactions with other residents and with the attendings. Interactions with the program director and the researcher were not mentioned. Interaction with patients was alluded to only by one resident. Interaction with nurses was mentioned by a few, and always as though nurses were inanimate objects.

Work scene: Roles as surgeon and as resident, their views of the program, the teaching methods, the teaching environment, the teaching taking place, and the learning being achieved were all discussed as concerns.

The individual interviews revealed similarities and differences among the residents that seemed to be related to personality rather than status in the residency hierarchy.

The attendings interviewed were cooperative and generally compliant. They spoke of their role as surgeon and teacher only, excluding interpersonal relationships and private life. They felt teaching occurred in the operating room by "doing." One attending felt questioning residents was an important tool of teaching and learning. Conferences and lectures were of secondary importance. Those attendings who mentioned nurses did so in the abstract, as inanimate objects or tools in surgical care.

Small-Group Discussions. Two groups of residents, "junior" and "senior," were identified. Junior residents included only those in postgraduate year 1 (PGY 1). Senior residents included all other residents, those in postgraduate years 2–5 (PGY 2–5). The chief resident, although a member of the senior resident group, was viewed differently because of his authority. The differentiation of the residents as junior or senior was corroborated by the language the staff used; they used the terms "we" and "they" to identify their own group and "the others."

Two small-group discussions were held with the junior residents, and three with the senior residents. The order of topics for discussion was chosen on the basis of degrees of sensitivity. The less sensitive issues—those of teaching and learning—were addressed first, then the more sensitive issue, interpersonal relationships at work.

The junior residents were different from the senior residents in that they were eager to participate in the identification of problems and solutions through the democratic process. They encouraged group participatation and mutual support. They were able to focus on teaching and learning in all phases of the program, and to voice positive suggestions for strengthening the program.

The senior residents, on the contrary, debated the issues, were resistant to any suggested change, felt that individual enterprise was most important, and tended to take over the discussion, debating their own agenda. All felt the attending surgeons were necessary, but potentially dangerous to their careers.

Large-Group Discussion. The attendings group discussion focused on teaching-learning. All agreed that the trainees were largely responsible for their own education, and that demonstration was more important than explanation. Most felt that interpersonal relationships were of limited importance, and that personal life was not a part of surgery.

The surgical service met, and the results were presented and discussed. The junior residents persisted in their request for more explanation in the teaching-learning process. The senior residents and attendings also persisted in their concept of teaching-learning through demonstration. All present were able to perceive the need for both elements.

Discussion

The method developed to study and change the surgical residency program is based on the self-disclosure technique (1). It is similar to standard small-group participatory methods (2) and structural brainstorming techniques (3, 4) but differs in two ways. First, topics for discussion in the small groups were chosen from themes revealed by individual interviews. Second, small-group discussions were orchestrated by two facilitators.

The ethnologist-researcher was the objective facilitator knowledgeable in the procedure. The program director and decision maker was the facilitator knowledgeable in the goals of surgical training. Traditionally, the ethnologist has simply observed the population to be studied and has described what was seen (5) and, the program director designs the training program according to modified Halsted tradition, consulting neither attendings nor trainees. The combination of ethnologist and program director as dual facilitators promotes exchange of information, increases awareness of attitudes and needs, and is a channel for change to occur. Through individual, undirected, open-ended interviews, insight was gained into each resident's background, style, attitude, and concerns. Using the information obtained, similarities and dissimilarities were identified. Groupings of similar concerns were used to define topics for the small-group discussions. Differences in themes among individuals appeared to be related to their personalities; this is a subject for future study.

The small groups allowed individuals at the same level to share their ideas, negotiate attitudes, arbitrate for change, support their own role needs, and collaborate to achieve their own ends. Junior residents were much more group-oriented. They were responsive to group suggestions, which were perceived as improvements to the program. Senior residents were individualistic in their problem solving, and independent in their conclusions. They felt that if there is a problem, "don't tell me how to solve it, I will do that myself."

A hierarchy of junior (PGY 1) and senior (PGY 2–5) residents became apparent, based on the perception of essentials in learning and teaching. The junior residents believed strongly in teaching by explanation, while the senior residents believed strongly in teaching by demonstration. The first-year residents, having just graduated from medical school, are used to the traditional classroom setting, where teaching-learning takes place through lectures. The senior residents, on the other hand, are used to the bedside, the operating room, or the emergency room, in which most of teaching-learning is done by showing how to do a procedure.

Large-group discussion allowed all members of the service to hear the attitudes and concerns of each small group. Since the residents were personally involved in the deliberation process, they became more open, their attitudes changed, their awareness was heightened, and they became facilitators of the arbitrated change in the program design. The attendings reacted similarly. The collaboration and involvement with open, nonthreatening exchange markedly reduces the potential adversary relationship between the trainee and the trainer. In addition, it improves the morale of the entire staff.

In previous ethnological studies of surgical training, there has been collaboration between the program people and the research anthropologist (5). What has been missing is a method of feedback to test the validity of observations (6). In this pilot study, themes for discussion for feedback allow identification of attitudes, perceptions, style needs, and problems in an objective way that tests their validity.

This approach is extremely valuable in assessing the design and management of a professional training environment. It is a resource for assessing any professional training program which can be applied once, or serially, to evaluate the effect of the arbitrated change.

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Health Services Research in Aging: What We Need to Know

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Setting Priorities. A small literature has developed on priorities for research in aging (1–8). Some favor priority for clinical problems like dementia that are common and cause substantial suffering. Others favor problems that, if solved, could provide new information to advance a basic science. Priority based on need implies that the problems of a class of persons are known and that solutions to these problems require critical missing information. Each of these conceptual schemes is open to the particular bias of persons setting the priorities.

In the early 1980s a panel, primarily academicians, organized to assist the National Institute for Aging (NIA) in the development of long-range plans for research on aging. The panel suggested that the major goals of research on aging were to understand the basic processes of aging; prevent and control the clinical manifestations of age and age-related disorders; understand the interactions between older people and society; and increase the opportunity for older persons to contribute productively to society. The results have been published as a National Plan for Research on Aging, a rich source of material on the present state of research in aging (7). A problem with the document is its failure to set priorities for the large number of research programs that it claims are needed. As Kane has commented, there are enough needed research projects in aging to employ an army of gerontologists and geriatricians; yet in 1978 only six academic physicians claimed geriatrics as their full-time specialty and research interest (1).

Since the medical, health care, and social service needs of elderly persons are well known, it should be possible to set priorities for research to meet these needs.

In one approach commonly used in industry but not widely used in health care research planning (9), research priority is a function of both problem importance and expected success. The ranking or priority setting is done by panels of experts in the field, using Delphi or group process methodologies.

This approach, however, has limitations. First, populations of older persons are highly variable socially and culturally; this fact limits generalizations. Second, experts and the elderly differ in how they rank problems. Impairments in sight or hearing are often felt by providers to be mild and relatively non-life-threatening, yet among the elderly themselves, these losses are often felt to be catastrophic. McNeil has shown that patients do not rank mortality and quality of life as physicians do; cancer patients offered laryngectomy valued preservation of speech more highly than the greater risk of recurrence, whereas physicians preferred the opposite ranking (10).

A Health Services Research Agenda

Health services research plans have been proposed by persons in academic geriatric medicine (1), the Veterans Administration (8), and health maintenance organizations (11). These plans reflect the needs of particular populations of older persons and the type of institution providing the care. Kelman has suggested areas of needed evaluative research in health planning and policy for the aged (12). Kane and his co-workers at the Rand Corporation and UCLA conclude that lack of knowledge in two areas is critical: how critical

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interventions affect the quality of care; and how the elderly, their families, and society value the outcomes of alternative geriatric and long-term care programs (1). From our own work and from the analyses of these authors we propose the following topics as a health services research agenda in gerontology.

Assessment. The evaluation of any strategy for improving the well-being of elderly persons requires accurate and appropriate assessment tools to measure health and functional status (13). Unfortunately, no agreement has been achieved on two crucial points: factors to be measured, and technology to make the measurements. Physical, mental, and social factors in the well-being of an elderly individual are so interrelated that multidimensional assessments of health status are necessary. Scales and measurement systems validated and proven reliable by widespread use in psychological and other experimentation need to be adapted for geriatric use. However, other measurement techniques need to be refined or developed (14).

Research with aging cohorts can provide useful data on the natural history of changes in health and function and in the use of services. An Alameda County study illustrates how subpopulations of aged persons can be defined and followed as distinct cohorts to provide such information (15).

Effectiveness of Care. Once a measurement capability has been established, geriatricians can begin to examine the effectiveness of clinical treatment and type of care. In long-term care, for example, investigators can show empirically the extent to which the overall goals—survival, independence, contentment, comfort, mental alertness— are compatible with one another and what trade-offs may be necessary. Alternatives to nursing home care, such as home care or day centers, may be significantly less expensive than institutional care. Whether they are more effective needs to be determined. It has been shown recently that patients served by a Geriatric Evaluation Unit had improvements in mortality, hospital readmission, and placement (16).

Iatrogenesis. Because elderly persons use many diagnostic and treatment services, they are especially vulnerable to iatrogenic complications (17). It is necessary to know to what extent medical intervention leads to a worsening of patients' conditions. Research is needed to assess the degree to which relatively sudden decline in health status is primarily or secondarily associated with diagnostic and therapeutic procedures, medications, or surgery, and to assess risk/benefit ratios for therapy, an issue not often considered in treating elderly patients. Adverse drug reactions, for example, occur more frequently in older persons, but it is unclear whether these reactions are due to inherent susceptibility, compliance problems, or inadequate education in the face of the combination of decreased memory and complex regimens.

Clinical Epidemiology. Many issues relevant to geriatric practive can be best approached from an epidemiologic perspective. For example, a few common problems account for a substantial proportion of the hospital admissions and long-term care days among the elderly. The most frequent causes for admission to geriatric wards in Britain are falls, strokes, incontinence, and mental confusion. The health services research scientist might investigate how the organization of services and the service delivery environment affect these problems, how social and environmental factors correlate with the prevalence of these common geriatric problems, and whether prevention programs are effective. For example, who is at risk for falls or incontinence, and what physiologic phenomena are associated with these events?

Case Management. The case manager, usually a nonphysician or a group of providers, organizes the best mix of social and medical services for the client, seeking to avoid inappropriate medicalization of social needs. Data from the Government Accounting Office study in Cleveland suggest that it is possible to classify both the care needed by and the services rendered to a population of elderly individuals (18). This study used a taxonomy that included a wide variety of medical and social services. The rate of change of status over time was related to the care received.

Community-based programs have tested the benefits of comprehensive assessment as a basis for patient planning in settings other than the nursing home. Two of the best-known programs, ACCESS in Rochester, NY, and TRIAGE in Connecticut, combine assessment and placement functions with periodic monitoring to estimate the appropriateness of placement.

It is not yet established that case management is less costly than conventional management of care.

Prevention. The prevention of disease and disability among the elderly is an active research area. Programs are now underway to explore whether early intervention with a variety of services can delay or avoid institutionalization. There is growing interest in improving the use of vaccines, and controlled trials of vaccination programs are needed. There are good reasons to expect that appropriate immunization will be cost-beneficial in the elderly (19). Enthusiasm is also building for early disease detection in the elderly, and criteria for useful screening tests have been defined (20). Careful trials are needed to identify areas in which early detection and intervention can alter the course of chronic illness. There is some basis for the fear that screening may actually have a negative effect by uncovering problems for which no effective intervention is available. Information is needed to describe the relationships between client characteristics, interventions, and benefits.

Personnel and the Organization of Care. The most critical issues in the organization of care for the aged are continuity and coordination, which are particularly jeopardized when patients must move between acute and long-term care. A number of studies look at new ways to coordinate long-term care (11). Their findings suggest that it is possible to substitute community and in-home support services for institutional care if proper coordination can be developed.

Until recently many health care providers—physicians and others—were not trained to deal effectively with elderly patients. Moreover, the growth of the elderly population has led to a perceived shortage of trained personnel. Recent research has assessed the role of health care teams; but, except for a single study by Kane and his co-workers, the cost-effectiveness of various groupings of health professionals in the care of the aged has not been demonstrated (21). Research is needed to evaluate the function of geriatric nurse-practitioners, physician assistants, social workers, mental health professionals, rehabilitation therapists, and others, including the most cost-effective staffing patterns for geriatric health care programs and the functions of health care teams. Careful research could also identify how, where, and to what degree self-care and family and volunteer systems can be effective medically and financially. The extent to which elderly persons are knowledgeable about their disabilities and diseases, and what the effect of increasing their understanding would be, have also not been clearly explored (22).

Ethics Research: A New Field. Medical ethics has until recently been considered a private matter for the individual practitioner. Physicians must now, by regulation or law, choose and defend in public their judgment about the correct balance between the physician–patient relation and defensive medical practice, between saving life and relieving suffering, and between allocating resources in the interests of patients and in line with the regulatory procedures of third-party payors.

The developing model of ethics research brings together the methods of social science, clinical research, and philosophy. Because the problems of geriatric care are interdisciplinary, such research will often involve collaboration between philosophers, legal scholars, physicians, and other clinicians.

One area of needed research in ethics concerns the use of Do-Not-Resuscitate (DNR) orders in hospital charts. Most DNR policies and guidelines recommend that before an order is written, the issues should be discussed with the patient and/or family. However, recent empirical studies of DNR practice suggest that this discussion is not often undertaken (22). Further research is needed to answer the question, Are there morally important obstacles to such discussion that ethicists are failing to consider, or does clinical practice simply need to catch up to current considered opinion? Brown and Thompson defined factors that correlated with decisions not to refer patients in nursing homes to acute care for pneumonia (24). Research is needed to determine the prevalence of this practice, and the role of families and staff in decision making.

Most ethics research has focused on hospitals and acute care. Also important is empirical research in nursing homes and other long-term care settings. Standards for decision making, involvement of residents and families, considerations of competance and informed consent, limits to paternalism, and the rights of families all carry a very different weight in long-term care, particularly at the end of life. The methods used by long-term care institutions to resolve difficult ethical dilemmas have not been described. Some nursing homes are turning to ethics committees to process these problems, but these committees may have no guidelines or policy. Research is needed to determine the effectiveness of these committees. A related need is the health outcomes that are most valued by elderly persons. Work on the measurement of value preferences with regard to health is only in its early stages (25).

Health Policy. Many of the problems of organizing medical care for the elderly persons could be solved, at least partially, by policy changes (26). Problems in reimbursement and resource allocation inherent in current Medicare, Medicaid, and health insurance provisions affect the organization and provision of services. For example, disease prevention and health promotion service are excluded from coverage by Medicare and many insurance providers. Little work has been published which carefully assesses the consequences of reimbursement policy on the care of the aged. While it can certainly be argued that the bias in the reimbursement system forces care into more expensive and less appropriate settings, the documentation of this assertion has just begun to accumulate. Demands for changes in Medicare, Medicaid, and other entitlement programs, such as the Veterans Administration health care system, will expand the need for this kind of research. For example, the implementation of fixed-rate reimbursement of hospitals by diagnosis-related group (DRG) may adversely affect the care of the elderly.

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Index to
Volume 52

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 52, No. 9, November 1985
Printed in U.S.A.

Index to Volume 52

Abdominal pregnancy causing massive lower gastrointestinal bleeding: case report, Salinas A, Guelrud M, Toledano A, Dreiling DA, 52(5):371–374.
Adelsberg B: Immunology of pregnancy 52(1):5–10.
Adrenergic response to cardiopulmonary bypass, Reves JG, 52(7):511–515.
Aggressive juvenile fibromatosis, Schwartz AM, Leonidas JC, Doku CH, 52(5):378–379.
Aguillaume CJ: *see* Thomas RI.
Ahmed A: *see* Tey PH.
Airan MC: *see* Skogerson KE.
Alter BP: *see* Kaye FJ.
Ambinder EP: *see* Kornfeld P.
Amelar S; *see* Lewis W.
Amniotic fluid microviscosity analysis in diabetic pregnancies: comparison with other methods of lung maturity assessment using predictive value analyses, Neufeld ND, Corbo L, Braunstein GD, Rasor J, 52(2):110–115.
Arbitrating change in staff attitudes and programs on a surgical service, Mathiot M, Williams JS, 52(9):
Arens JF: Three decades of cardiac anesthesia, 52(7):516–520.
Artificial intelligence methods for expert medical consultant systems, Kulikowski CA, 52(2):87–93.
Aufses AH: Management of colorectal cancer, 52(3):172–175; *see* also Loiterman DA.
Autopsy findings as modifier of diagnosis-related-group classification and hospital reimbursement, Heller J, Friedlander D, Geller SA, 52(5):311–314.
Awards, The Mount Sinai Journal, 1984/85, 52(6):414–415.
Azathioprine experience in severe, generalized, recalcitrant myasthenia gravis, Kornfeld P, Ambinder EP, Matta R, Bender A, Papatestas AE, Gross H, Genkins G, 52(5):347–352.

Barash PG: *see* Hines R.
Basic research and its potentials of relevance, Merton RK, Moss JZ, 52(9):
Basile F: *see* Romeo G.
Bauer J: *see* Salky B.
Behar AJ: *see* Ilie B.
Bekesi G: *see* Tsang PH.
Belville R, Florman D, Nechemias C: Health services research in action: explaining a decrease in patient visits at a diabetes clinic, 52(9): 702–707.
Belville R, Moss JZ: Role of social scientist in planning and implementing change in a medical center, 52(9):724–730.
Belville R: *see* Moss JZ.
Benjamin E: *see* Raskin JM.
Berger SA: postoperative pain control: review of methods, 52(2):142–147.
Berk AA: *see* Sacks HS.
Berkowitz GS: Clinical and obstetric risk factors for preterm delivery, 52(4):239–247.
Berkowitz RL: *see* Chevenak FA.
Berman ND: Valvular heart disease in the elderly, 52(8):594–600.
Beta adrenergic blocking agents: review and update, Squire A, Kupersmith J, 52(7):553–558.
Bierman HR: Multiple primary neoplasms and tumor diathesis, 52(6):435–442.
Biller HR: Conservation surgery of the larynx, 52(3):191–192.
Borek E: *see* Fischbein A.
Bosch SJ, Merino R, Rose D, Deuschle K: Can academic medical center health services research be useful in community development? 52(9):744–748.
Bowers CH: *see* Dorfman SF.
Brain biopsy: risks, benefits, and indications, Sevush S, Turkewitz LJ, 52(5):380–383.
Braunstein GD: *see* Edwards TH, Neufeld ND.
Breast cancer: which operation? Papatestas AE, 52(3):181–183.
Brodheim E: Preliminary remarks, Computer in clinical decision making, 52(2):80–81.

Cali R: *see* Romeo G.
Can academic medical center health services research be useful in community development? Bosch SJ, Merino R, Rose D, Deuschle K, 52(9):744–748.
Cancer chemotherapy: past is prologue, Martin DS, 52(6):426–434.
Cancer surgery: the view from cancer medicine, Holland JF, 52(3):159–160.
Cardiac anesthesia: three decades, Silvay G, guest ed., 52(7):499–564.
Cardiac arrhythmias in the elderly: selected aspects, Dolgin M, 52(8):601–609.
Cardiac problems in elderly patients: early recognition and management, Kleinfeld M, guest ed., 52(8):579–643.
Cardi F: *see* Romeo G.
Cardiotoxic effects of chemicals, Horowitz SF, Matza D, Machac J, 52(8):650–655.
Carroll HJ: *see* Uribarri.
Caruso U, Elli M, Cravoto E, Tisone G, Lombardo PA, Silvaroli M, Ficorella C, Cortesi E, Casciani CU: Colorectal cancer (Dukes group B2, C1, C2): adjuvant chemotherapy and toxicity, 52(6):470–472.
Casciani CU: *see* Caruso U.
Case report: milk of calcium in the kidney after cyst puncture, Tey PH, Ahmed A, Chan KF, 52(8):659–660.
Case report: ultrasonographic features of "milk of calcium" in kidney, Diakoumakis E, Vieux U, Seife B, Snyder TC, 52(8):656–658.
Casley-Smith JR: Letter to the editor: importance of the lymphatic system, 52(8):671.
Cassel C: *see* McCally M.
Catania G: *see* Romeo G.
Cesarean section patterns: influence of a perinatology service, Gleicher N, Vermesh M, Rotmensch Z, Thornton J, Elrad H, 52(2):100–105.
Chalmers TC: *see* Sacks HS.
Chan KF: *see* Tey PH.
Charnoff SK: Radiology notes, case 1 52(2):133–135.
Cherry S, guest ed., Medical, surgical, and gynecologic complications of pregnancy, 52(1):1–77; Introduction, 52(1):1–2.
Chervenak FA, Berkowitz RL: Hypertension in pregnancy, 52(1):46–58.

Clinical and obstetric risk factors for preterm delivery, Berkowitz GS, 52(4):239–247.
Clinical aspects of gestational trophoblastic diseases, Runowicz CD, 52(1):35–45.
Clinical epidemiology, Mulvihill MN, Skovron ML, guest eds, 52(4):234-309. Introduction 52(4):234–235.
Cobin R: *see* Davies TF.
Colorectal cancer (Dukes group B2, C1, C2): adjuvant chemotherapy and toxicity, Caruso U, Elli M, Cravotto E, Tisone G, Lombardo PA, Silvaroli M, Ficorella C, Cortesi E, Casciani CU, 52(6):470–472.
Combination cancer chemotherapy, Waxman S, guest ed., 52(6):405–469. Introduction, 52(6):417–418.
Combination chemotherapy of breast cancer, Cooper RG, 52(6):443–446.
Computer as a new basis for analytic clinical practice: coupling individual problems with medical knowledge, Weed LL, 52(2):94–99.
Computer in clinical decision making, Wolf CW, guest ed., 52(2):79–157.
Confino E: *see* Ismajovich.
Conservation surgery of the larynx, Biller HR, 52(3):191–192.
Constraints in the development of a rural primary health care program in the Dominican Republic, Fischer E, Merino R, 52(9):719–723.
Coombs' positive hemolytic anemia following sulfasalazine therapy in ulcerative colitis: case reports, review, and discussion of pathogenesis, Mechanick JI, 52(8):667–670.
Cooper RG: Combination chemotherapy of breast cancer 52(6):443–446.
Corbo L: *see* Neufeld ND.
Cornbill R, Foner P, Halper DE: Evaluating a proposed change in a delivery system and reimbursement structure case study of planning for a hospital, 52(9):708–713.
Corre KA, Hansen JE, Rothstein RJ: Nomograms for predicted FEV_1 and FVC in children, adolescents, and adults, 52(5):315–318.
Cortesi E: *see* Caruso U.
Cravotto E: *see* Caruso U.
Crohn's disease and pregnancy: literature study, Gennuso R, 52(5):398–403.
Current status and new vistas in combination chemotherapy Frei E, 52(6):460–464.
Current therapy of demyelinating neuropathies, Ruderman MI, Turkewitz JL, 52(6):490–495.
Cystic islet cell tumor: diagnosis and surgical management, Loiterman DA, Schwartz IS, Aufses AH, 52(3):212–215.
Cytomegalovirus infection and hemolytic anemia due to glucose-6-phosphate dehydrogenase deficiency, Rosenbloom BE, Rosenfelt FP, Ullman H, Weinstein IM, 52(5):363–366.

Dana BS: Education in community medicine: Perspective, 52(4):282–283.
Dan SJ: *see* Lewin B, Lidov M.
Davey PG, McGuinness EE, Nicol S, Wormsley KG: Experimental colitis and colonic cancer in the rat, 52(3):209–211.
David MP: *see* Ismajovich B.
Davidson MB: *see* Edwards TH.
Davies TF, Cobin R: Thyroid disease in pregnancy and the postpartum period, 52(1):59–77.
Davis S: Private-sector health care initiatives, 52(6):409–413.
Deep hypothermic circulatory arrest: current status and future directions, Hickey PR, 52(7):541–547.
Deluca E: *see* Torino FD.
Deuschle KW: Epidemiology at Mount Sinai School of Medicine: Perspective, 52(4):237–238; Perspective: health services research at The Mount Sinai Medical Center, 52(9):677–678; *see* also Bosch SJ.
Development and application of a productivity data base for hospitals, Kundel CD, 52(9):714–718.
Diakoumakis E, Vieux U, Seife B, Snyder TC: Case report: ultrasonographic features of "milk of calcium" in kidney, 52(8):656–658.
Discussion, Breast cancer: Which operation? Papatestas AE, 52(3):184.
Doku CH: *see* Schwartz AM.
Dolgin M: Cardiac arrhythmias in the elderly: selected aspects, 52(8):601–609.
Dorfman SF, Bowers CH: Rubella susceptibility among prenatal and family planning clinic populations, 52(4):248–252.
Doses to organs at risk from mantle field radiation therapy using 10 MV X-rays, Wong PS, Rosemark PJ, Wexler MC, Greenberg SH, Thompson RW, 52(3):216–220.
Dreiling DA, Koller M: Natural history of alcoholic pancreatitis: update 1985, 52(5):340–342.
Dreiling DA, Triebling A, Koller M: Effect of age on human exocrine pancreatic secretion, 52(5):336–339.
Dreiling DA: *see* Salinas A.
Dula E, Konsens R: Etiology of primary spontaneous pneumothorax, 52(7):575–578.

Education in community medicine: Perspective, Dana BS, 52(4):282–283.
Edwards TH, Braunstein GD, Davidson MB: Glyburide-induced hypoglycemia in an elderly patient: similarity of first-generation and second-generation sulfonylurea agents, 52(8):644–646.
Effect of age on human exocrine pancreatic secretion Dreiling DA, Triebling AT, Koller M, 52(5):336–339.
Ehr AP: *see* Mulvihill MN.
Electrocardiographic patterns of normally functioning dual chamber pacemakers, Tolentino AO, Javier RP, Samet P, 52(2):116–122.
Eliasberg BH: photograph, 52(7): facing page 499.
Elli M: *see* Caruso U.
Elrad H: *see* Gleicher N.
Endocrine response to cardiopulmonary bypass, Philbin DM 52(7):508–510.
Endocrinology of pregnancy, Kase NG, Reyniak JV, 52(1):11–34.
Enteropancreatic reflexes 2: effect of jejunal distension, Salinas A, Klein E, Toth L, Dreiling DA, 52(5):331–335.
Environmental Medicine Notes, Fischbein A, ed., Cardiotoxic effects of chemicals, Horowitz, SF, Matza D, Machac J, 52(8):650–655; Modified nucleosides and early detection of occupational cancer: a challenge for the future, Fischbein A, Sharma OK, Borek E, 52(6):480–483; New dimensions in occupational medicine, Fischbein A, 52(6):478–479.
Epidemiology at Mount Sinai School of Medicine: Perspective, Deuschle KW, 52(4):237–238.
Error rate factor in the management of suspected acute appendicitis: has anything changed? Mockapetris AM, 52(4):297–305.
Estafanous FG: Role of some noncardiac factors in determining hemodynamic alterations during cardiac surgery, 52(7):559–564.
Evaluating a proposed change in a delivery system and reimbursement structure: case study of planning for a hospital, Cornbill R, Foner P, Halper DE, 52(9):708–713.
Experimental and clinical studies with serve-controlled glucose and insulin administration during cardiopulmonary bypass, Galletti PM, Kuntschen FR, Hahn C, 52(7):500–507.
Experimental colitis and colonic cancer in the rat, Davey PG, McGuinness EE, Nicol S, Wormsley KG, 52(3):209–211.

Factors predicting survival for six months after cardiopulmonary resuscitation: multivariate analysis of a prospective study, Skovron ML, Goldberg E, Suljaga-Petchel K, 52(4):271–275.
Factors predisposing to intraoperative myocardial infarction

during coronary artery bypass surgery, Schneider RR, Pichard AD, Mindich B, 52(2):123–129.
Falkenstein J: *see* Mulvihill MN.
Ficorella C: *see* Caruso U.
Fischbein A: New dimensions in occupational medicine, 52(6):478–479.
Fischbein A, Sharma OK, Borek E: Modified nucleosides and early detection of occupational cancer: a challenge for the future, 52(6):480–483.
Fischbein A: Environmental Medicine Notes ed. *see* Environmental Medicine Notes.
Fischer E, Merino R: Constraints in the development of a rural primary health care program in the Dominican Republic, 52(9):
Florman D: *see* Belville R.
Foner P: *see* Cornbill R.
Forley BG: Protein-calorie malnutrition, immunological function, and total parenteral nutrition in the surgical patient, 52(2):148–157.
Forward to 3rd ed. Medical, surgical, and gynecologic complications of pregnancy, Gusberg S, 52(1):3.
Frayer WW: Information management systems in neonatal intensive care: a case report, 52(2):82–86.
Fredland AJ: *see* Skogerson KE.
Frei E: Current status and new vistas in combination chemotherapy, 52(6):460–464.
Friedlander D: *see* Heller J.
Friedman G: New drugs in gastroenterology, 52(6):484–489.
Fuster V, Griepp PR: Tetralogy of fallot: historical lessons, 52(7):534–540.

Gale JT, Schlusselberg D: Radiology notes, case 2, 52(2):136–138.
Galletti PM, Kuntschen FR, Hahn C: Experimental and clinical studies with serve-controlled glucose and insulin administration during cardiopulmonary bypass, 52(7):500–507.
Garaycoechea ME: *see* Torino FD.
Gastric inflammatory pseudotumor, Skogerson KE, Friedland AJ, Airan MC, 52(8):661–662.
Gastric neurilemmoma: case report, Pinto AS, Novo JAP, 52(8):647–649.
Gastroenterology Notes: Sachar DB, ed., New drugs in gastroenterology, Friedman G, 52(6):484–489.
Gelernt I: *see* Salky B.
Geller SA: *see* Heller J.
Genkins G: *see* Kornfeld P.
Gennuso R: Crohn's disease and pregnancy: literature study, 52(5):398–403; photograph, 52(6):414; student award 1984/85, 52(6):414.
Gerber M: *see* Wasser WG.
Giannone G: *see* Romeo G.
Gibson G: Research settings and health services research: does where you do it affect who listens? 52(9):
Giovinetto A: *see* Romeo G.
Gleicher N, Vermesh M, Rotmensch Z, Thornton J, Elrad H: Cesarean section patterns: influence of a perinatology service, 52(2):100–105.
Gleischman SH: Multiple synchronous scar-related lung carcinomas; case report and review, 52(7):565–568.
Glenn JF: Introduction: new frontiers in surgical oncology, 52(3):158; Medical manpower and other strategic issues, 52(6):405–408.
Glenn JF, Grupenhoff JT, Levinson PS: Seminars for Congressional aides: an educational program on the role of the urban academic medical center, 52(9):736–739.
Globus Award 1984/85: Kuhn M, 52(6):415; Wallace DJ, 52(6):415.
Glyburide-induced hypoglycemia in an elderly patient: similarity of first-generation and second-generation sulfonylurea agents, Edwards TH, Braunstein GD, Davidson MB, 52(8):644–646.
Goddeeris J, Weisbrod BA: What we don't know about why health expenditures have soared: interactive effects of insurance and technology, 52(9):
Goldberg E: *see* Skovron ML.
Goldin A: Preclinical chemotherapy: historical aspects, 52(6):419–425.
Goldman M: *see* Konstadt S.
Goldstein MH: *see* Wasser WG.
Gombos GM: *see* Levitan M.
Gomes JA: Sinus node dysfunction: new concepts and evaluation of patients with suspected sick sinus syndrome 52(8):610–617.
Grady RF: Noncardiac surgery in the elderly patient with heart disease, 52(8):634–643.
Greenberg SH: *see* Wong PS.
Green SJ, Ong LY, Reiser P, Morrison J: Role of early radionuclide ejection fraction in predicting early mortality after acute myocardial infarction in the elderly, 52(8):618–622.
Greenspan EM: photograph, 52(6):416; Prior tuberculosis in long-term survivors of breast and ovarian cancer from a New York oncology practice (1954–1974), 52(6):465–469.
Griepp RB: *see* Fuster V.
Grishman E: *see* Wasser WG.
Gross H: *see* Kornfeld P.
Grupenhoff JT: *see* Glenn JF.
Guelrud M: *see* Salinas A.
Gusberg S: Forward to 3rd ed., Medical, surgical, and gynecologic complications of pregnancy, 52(1):3.

Hahn C: *see* Galletti PM.
Halper DE: *see* Cornbill R.
Hammond D: *see* Mandelblatt JS.
Hansen JE: *see* Corre KA.
Health services research for hospital policy, Moss JZ, Belville R, 52(9):693–701.
Health services research in action: explaining a decrease in patient visits at a diabetes clinic, Belville R, Florman D, Nechemias C, 52(9):702–707.
Health services research in aging, McCally M, Cassel C, 52(9):753–757.
Health Services Research, Moss JZ, Belville R, guest eds., 52(9):672–756; Introduction: 52(9):672–676.
Heller J, Friedlander D, Geller SA: Autopsy findings as modifier of diagnosis-related-group classification and hospital reimbursement, 52(5):311–314.
Hepatocellular carcinoma presenting as sphenoid sinus metastasis, Waxman JS, Seife B, Waxman M, 52(3):221–224.
Hickey PR: Deep hypothermic circulatory arrest: current status and future directions, 52(7):541–547.
High-dose combination chemotherapy: why, how, and when, Israel L, 52(6):447–451.
Hill BT: *see* Price LA.
Hines R, Barash PG: Right ventricular function in the perioperative period, 52(7):529–533.
Holland JF: Cancer surgery: the view from cancer medicine, 52(3):159–160; *see* Tsang PH.
Holland JF, Waxman S: Introduction, Combination cancer chemotherapy, 52(6):417–418.
Hollander V: Prostate cancer: Clinical trials of gonadotrophin-releasing hormone analogs as an alternative to orchiectomy, 52(3):205–206.
Horowitz SF, Matza D, Machac J: Cardiotoxic effects of chemicals, 52(8):650–655.
Hypertension in pregnancy, Chervenak FA, Berkowitz RL, 52(1):46–58.
Hypertension in the elderly, Uribarri J, Oh M, Carroll HJ, 52(8):581–593.

Iberti TJ: *see* Raskin JM.
Idiopathic pulmonary hemosiderosis: importance of chest radiograph in children with unexplained anemia, Kuhn MJ, 52(5):358–362.

Ilie B, Behar AJ: Solitary neurofibroma of the gall bladder: report of three cases and literature review, 52(6):473–477.
Immune complexes in cancer and preneoplastic diseases, Shafir M, 52(3):201–204.
Immunology of pregnancy, Adelsberg B, 52(1):5–10.
Improved method to test the completeness of parietal cell vagotomy, Romeo G, Giovinetto A, Cali R, Basile F, Catania G, Cardi F, Giannone G, 52(5):324–325.
Inferior vena cava interruption, Keller SM, Papa M, Wilder JR, 52(5):353–357.
Information management systems in neonatal intensive care: a case report, Frayer WW, 52(2):82–86.
Interventional radiology of the biliary tree: Introduction, Train JS, 52(5):387–388.
Intraoperative diagnosis of myocardial ischemia, Konstadt S, Goldman M, Thys D, Mindich BP, Kaplan JA, 52(7):521–525.
Introduction: New frontiers in surgical oncology, Glenn JF, 52(3):158.
Ismajovich B, Confino E, Sherzer A, Lidor AL, David MP: Optimal delivery of nonvertex twins, 52(2):106–109.
Israel L: High-dose combination chemotherapy: why, how and when, 52(6):447–451.

Javier RP: *see* Tolentino AO.
Jones RB: Treatment of hepatic metastases, 52(3):176–180.

Kaneko M: *see* Unger PD.
Kaplan JA: *see* Konstadt S.
Kaplan MH: Stress, pancreatic perfusion, and acute pancreatitis: unified concept of pathogenesis, 52(5):326–330.
Kase NG, Reyniak JV: Endocrinology of pregnancy, 52(1):11–34.
Kaye FJ, Alter BP: Red-cell size distribution analysis: evaluation of microcytic anemia in chronically ill patients, 52(5):319–323.
Keller SM, Papa M, Wilder JR: Inferior vena cava interruption, 52(5):353–357.
Klein E: *see* Salinas A.
Kleinfeld M, guest ed., Cardiac problems in elderly patients: early recognition and management, 52(8):579–643; Introduction, 52(8):579–580.
Koffsky RM: *see* Silvay G.
Koller M: *see* Dreiling DA.
Konsens R: *see* Dula E.
Konstadt S, Goldman M, Thys D, Mindich BP, Kaplan JA: Intraoperative diagnosis of myocardial ischemia, 52(7):521–525.
Kornfeld P, Ambinder EP, Matta R, Bender A, Papatestas AE, Gross H, Genkins G: Azathioprine experience in severe, generalized, recalcitrant myasthenia gravis, 52(5):347–352.
Kreel I: *see* Salky B.
Kuhn MJ: Globus award 1984/85, 52(6):415; Idiopathic pulmonary hemosiderosis: importance of chest radiograph in children with unexplained anemia, 52(5):358–362; photograph, 52(6):415.
Kulikowski CA: Artificial intelligence methods for expert medical consultant systems, 52(2):87–93.
Kundel CD: Development and application of a productivity data base for hospitals, 52(9):714–718.
Kuntschen FR: *see* Galletti PM.
Kupersmith J: *see* Squire A.

Laparoscopy for gastrointestinal diseases, Salky B, Bauer J, Gelernt I, Kreel I, 52(3):228–232.
Lefkowitz P, Suljaga-Petchel K: Prevalence of alcoholism in acute-care general hospital patients, 52(4):291–296.
Leonidas JC: *see* Schwartz AM.
Letter to the editor: importance of lymphatic system, Casley-Smith JR, 52(8):671.
Levinson PS: *see* Glenn JF.
Levitan H: *see* Levitan M.
Levitan LJ: *see* Levitan M.
Levitan M, Gombos GM, Levitan H, Levitan LJ: Senile macular degeneration and Kuhnt-Junius degeneration as separate entities: review, 52(8):663–666.
Lewin B, Train JS, Dan SJ, Mitty HA: Percutaneous transhepatic removal of a giant bile-duct stone, 52(5):389–391.
Lewis W: Photograph, 52(6):414; The Mount Sinai Journal Award 1984/85, 52(6):414.
Lidor AL: *see* Ismajovich B.
Lidov M, Train JS, Dan SJ, Mitty HA: Percutaneous transhepatic dilation of a choledochoenterostomy stricture, 52(5):392–394.
Liftin AJ: Nonmedullary carcinoma of the thyroid gland in association with amyloid goiter: case report, 52(3):224–227.
Loiterman DA, Schwartz IS, Aufses AH: Cystic islet cell tumor: diagnosis and surgical management, 52(3):212–215.
Lombardo PA: *see* Caruso U.
Lymphatic system (letter), Casley-Smith JR, 52(8):671.

McCally M, Cassel C: Health services research in aging, 52(9):753–757.
McGuinness EE: *see* Davey PG.
Machac J: *see* Horowitz SF.
McQuay RM: Profile of a successful hospital clinical parasitology laboratory, 52(5):384–386.
Malignant fibrous histocytoma of the maxillary sinus, Unger PD, Kaneko M, Thung SH, 52(7):569–574.
Malignant histiocytosis, Plous R, 52(6):496–498.
Management of colorectal cancer, Aufses AH, 52(3):172–175.
Management of depression and anxiety following myocardial infarction, Stern TA, 52(8):623–633.
Mandelblatt JS, Hammond D: Primary care of elderly women: is Pap smear screening necessary? 52(4):284–290.
Martin DS: Cancer chemotherapy: past is prologue, 52(6):425–434.
Mathiot M, Williams JS: Arbitrating change in staff attitudes and programs on a surgical service, 52(9):749–752.
Matta R: *see* Kornfeld P.
Matza D: *see* Horowitz SF.
Mechanical support of the failing heart, Silvay G, Koffsky RM, 52(7):548–552.
Mechanick JI: Coombs'-positive hemolytic anemia following sulfasalazine therapy in ulcerative colitis: case reports, review, and discussion of pathogenesis, 52(8):667–670.
Medical manpower and other strategic issues, Glenn JF, 52(6):405–408.
Medical, surgical, and gynecologic complications of pregnancy, Cherry S, guest ed., 52(1):1–77.
Merino R: *see* Bosch SJ; Fischer E.
Merton RK, Moss JZ: Basic research and its potentials of relevance, 52(9):
Mindich BP: *see* Konstadt S.; Schneider RR.
Mitty HA: *see* Lewin B.; Lidov M.; Stollman AL.
Mockapetris AM: Error rate factor in the management of suspected acute appendicitis: has anything changed? 52(4):297–305.
Modified nucleosides and early detection of occupational cancer: a challenge for the future, Fischbein A, Sharma OK, Borek E, 52(6):480–483.
Monitoring the left ventricle: volume versus pressure, Thys DM, 52(7):526–528.
Morrison BJ: *see* Rosenberg G.
Morrison J: *see* Green SJ.
Moss JZ: *see* Belville R.; Merton RK.
Moss JZ, Belville R, guest eds., Health services and social research, 52(9):672–757; Health services research for hospital policy, 52(9):693–701; Introduction 52(9):672–676.

Mount Sinai Journal Award 1984/85: Lewis W, Amelar S, Puszkin S, 52(6):414.

Mount Sinai Journal, The: presents 1984/85 awards to authors, 52(6):414–415; receives Sandoz award for 1984, 52(6):415.

Multiple primary neoplasms and tumor diathesis, Bierman HR, 52(6):435–442.

Multiple synchronous scar-related lung carcinomas: case report and review, Gleischman SH, 52(7):565–568.

Mulvihill MN, Skovron ML: guest eds., Clinical epidemiology: 52(4):234–235.

Mulvihill MN, Suljaga-Petchel K, Falkenstein J, Ehr AP: Patterns of diazepam prescribing in primary care: case control study, 52(4):276–281.

Natural history of alcoholic pancreatitis: update 1985, Dreiling DA, Koller M, 52(5):340–342.

Nechemias C: *see* Belville R.

Neufeld ND, Corbo L, Braunstein GD, Rasor J: Amniotic fluid microviscosity analysis in diabetic pregnancies: comparison with other methods of lung maturity assessment using predictive value analyses, 52(2):110–115.

Neurology Notes, Turkewitz LJ, ed.: Current therapy of demyelinating neuropathies, Ruderman MI, Turkewitz JL, 52(6):490–495.

New dimensions in occupational medicine, Fischbein A, 52(6):478–479.

New drugs in gastroenterology, Friedman G, 52(6):484–489.

Newton M, Zinn KM: Postcryotherapy dellen formation in diabetics with proliferative retinopathy, 52(2):130–132.

Nicol S: *see* Davey PG.

Nomograms for predicted FEV_1 and FVC in children, adolescents, and adults, Corre KA, Hansen JE, Rothstein RJ, 52(5):315–318.

Noncardiac surgery in the elderly patient with heart disease, Grady RF, 52(8):634–643.

Nonmedullary carcinoma of the thyroid gland in association with amyloid goiter: case report, Liftin AJ, 52(3):225–227.

Norton L: Thoughts on the surgical staging of lymphomas, 52(3):185–188; Tumor growth kinetics, 52(3):161–164.

Novo JAP: *see* Pinto AS.

Oh M: *see* Uribarri.

Ong LY: *see* Green SJ.

Ophthalmology Notes: Postcryotherapy dellen formation in diabetics with proliferative retinopathy, Newton M, Zinn KM, 52(2):130–132.

Optimal delivery of nonvertex twins, Ismajovich B, Confino E, Sherzer A, Lidor AL, David MP, 52(2):106–109.

Orthopedic oncology, Sherry HS, 52(3):189–190.

Papa M: *see* Keller SM.

Papatestas AE: Breast cancer: Which operation? 52(3):181–183; Discussion, 184; *see* Kornfeld P.

Pathology Notes: Profile of a successful hospital clinical parasitology laboratory, McQuay RM, 52(5):384–386.

Patterns of diazepam prescribing in primary care: case control study, Mulvihill MN, Suljaga-Petchel K, Falkenstein J, Ehr AP, 52(4):276–281.

Percutaneous transhepatic dilation of a choledochoenterostomy stricture, Lidov M, Train JS, Dan SJ, Mitty HA, 52(5):392–394.

Percutaneous transhepatic placement of a biliary endoprosthesis, Stollman AL, Train JS, Dan SJ, Mitty H, 52(5):395–397.

Percutaneous transhepatic removal of a giant bile-duct stone, Lewin B, Train JS, Dan SJ, Mitty HA, 52(5):389–391.

Perera SG: *see* Torino FD.

Perspective: health services research at The Mount Sinai Medical Center, Deuschle KW, 52(9):677–678.

Philbin DM: Endocrine response to cardiopulmonary bypass 52(7):508–510.

Photograph: Eliasberg BH, 52(7): facing page 499; Gennuso R, 52(6):414; Greenspan EM, 52(6):416; Kuhn MJ, 52(6):415; Lewis W, 52(6):414; Wallace DJ, 52(6):415.

Pichard AD: *see* Schneider RR.

Pinto AS, Novo JAP: Gastric neurilemmoma: case report, 52(8):647–649.

Plous R: Malignant histiocytosis, 52(6):496–498.

Portillo NA: *see* Torino FD.

Postcryotherapy dellen formation in diabetics with proliferative retinopathy, Newton M, Zinn KM, 52(2):130–132.

Postoperative pain control: review of methods, Berger SA 52(2):142–147.

Preclinical chemotherapy: historical aspects, Goldin A, 52(6):419–425.

Preliminary observation on application of ethibloc in necrohemorrhagic acute pancreatitis in humans, Torino FD, Portillo NA, Romero OA, Garaycoechea ME, Deluca E, Perera SG, 52(5):343–346.

Preliminary remarks, Computer in clinical decision making, Brodheim E, 52(2):80–81.

Prevalence of alcoholism in acute-care general hospital patients, Lefkowitz P, Suljaga-Petchel K, 52(4):291-296.

Price LA, Hill BT: Safer combination chemotherapy using a kinetically based experimental approach, 52(6):452–459.

Primary care of elderly women: is Pap smear screening necessary? Mandelblatt JS, Hammon D, 52(4):284–290.

Prior tuberculosis in long-term survivors of breast and ovarian cancer from a New York oncology practice (1954–1974), Greenspan EM, 52(6):465–469.

Private-sector health care initiatives, Davis S, 52(6):409–413.

Profile of a successful hospital clinical parasitology laboratory, McQuay RM, 52(5):384–386.

Prostate cancer: Clinical trials of gonadotrophin-releasing hormone analogs as an alternative to orchiectomy, Hollander V, 52(3):205–206.

Protein-calorie malnutrition, immunological function, and total parenteral nutrition in the surgical patient, Forley BG, 52(2):148–157.

Puszkin S; *see* Lewis W.

Rabinowitz JG: Radiology Notes ed. *see* Radiology Notes.

Radiology Notes: Case 1, Charnoff SK, 52(2):133–135; Case 2, Gale JT, Schlusselberg D, 52(2):136–138; Case report: milk of calcium in the kidney after cyst puncture, Tey PH, Ahmed A, Chan KF, 52(8):659–660; Case report: ultrasonographic features of "milk of calcium" in kidney, Diakoumakis E, Vieux U, Seife B, Snyder TC, 52(8):656–658; Interventional radiology of the biliary tree: Introduction, Train JS, 52(5):387–388; Percutaneous transhepatic dilation of a choledochoenterostomy stricture, Lidov M, Train JS, Dan SJ, Mitty HA, 52(5):392–394; Percutaneous transhepatic placement of a biliary endoprosthesis, Stollman AE, Train JS, Dan SJ, Mitty H, 52(5):395–397; Percutaneous transhepatic removal of a giant bile-duct stone, Lewin B, Train JS, Dan SJ, Mitty HA, 52(5):389–391.

Raskin JM, Benjamin E, Iberti TJ: Venous air embolism: case report and review, 52(5):367–370.

Rasor J: *see* Neufeld ND.

Recurrent nephropathy associated with heroin use, Wasser WG, Grishman E, Goldstein MH, Gerber M, 52(5):375–376.

Red-cell size distribution analysis: evaluation of microcytic anemia in chronically ill patients, Kaye FJ, Alter BP, 52(5):319–323.

Refusal of treatment: role of psychiatric consultation, Stam M, Strain JJ, 52(4):306–309.

Rehr H: *see* Rosenberg G.

Reiser P: *see* Green SJ.
Reitman D: *see* Sacks HS.
Research settings and health services research: does where you do it affect who listens? Gibson G, 52(9):731–735.
Reves JG: Adrenergic response to cardiopulmonary bypass 52(7):511–515.
Reyniak JV: *see* Kase NG.
Right ventricular function in the perioperative period, Hines R, Barash PG, 52(7):529–533.
Role of early radionuclide ejection fraction in predicting early mortality after acute myocardial infarction in the elderly, Green SJ, Ong LY, Reiser P, Morrison J, 52(8):618–622.
Role of research when a biomedical issue is politicized: regulation of methadone maintenance, Thomas RI, Aguillaume CJ, 52(9):740–743.
Role of social scientists in planning and implementing change in a medical center, Belville R, Moss JZ, 52(9):724–730.
Role of some noncardiac factors in determining hemodynamic alterations during cardiac surgery, Estafanous FG, 52(7):559–564.
Romeo G, Giovinetto A, Cali R, Basile F, Catania G, Cardi F, Giannone G: Improved method to test completeness of parietal cell vagotomy, 52(5):324–325.
Romero OA: *see* Torino FD.
Rose DN, Silver AL, Schechter CB: Tuberculosis chemoprophylaxis for diabetics: are the benefits of isoniazid worth the risk? 52(4):253–258.
Rose DN: *see*Bosch SJ.
Rosenberg G, Speedling EJ, Rehr H, Morrison BJ: Some effects of a hospital employee strike on patient satisfaction, 52(4):259–264.
Rosenbloom BE, Rosenfelt FP, Ullman H, Weinstein IM: Cytomegalovirus infection and hemolytic anemia due to glucose-6-phosphate dehydrogenase deficiency, 52(5):363–366.
Rosenfelt FP: *see* Rosenbloom BE.
Rosen-Levin EM, Schwartz IS: Solitary cecal ulcer due to cytomegalovirus in a leukemic patient, 52(2):139–141.
Rosemark PJ: *see* Wong PS.
Rothstein RJ: *see* Corre KA.
Rotmensch Z: *see* Gleicher N.
Rovinsky J, Introduction to issue, Medical, surgical, and gynecologic complications of pregnancy, 52(1):2.
Rubella susceptibility among prenatal and family planning clinic populations, Dorfman SF, Bowers CH, 52(4):248–252.
Ruderman MI, Turkewitz LJ: Current therapy of demyelinating neuropathies, 52(6):490–495.
Runowicz CD: Clinical aspects of gestational trophoblastic diseases, 52(1):35–45.

Sachar DB: Gastroenterology Notes ed., *see* Gastroenterology Notes.
Sacks HS, Chalmers TC, Berk AA, Reitman D: Should mild hypertension be treated? An attempted meta-analysis of the clinical trials, 52(4):265–270.
Safer combination chemotherapy using a kinetically based experimental approach, Price LA, Hill BT, 52(6):452–459.
Salinas A, Guelrud M, Toledano A, Dreiling DA: Abdominal pregnancy causing massive lower gastrointestinal bleeding: Case report, 52(5):371–374.
Salinas A, Klein E, Toth L, Dreiling DA: Enteropancreatic reflexes 2: effect of jejunal distension, 52(5):331–335.
Salky B, Bauer J, Gelernt I, Kreel I: Laparoscopy for gastrointestinal diseases, 52(3):228–232.
Samet P: *see* Tolentino AO.
Sandoz award to The Mount Sinai Journal: 52(6):415.
Schechter CB: *see* Rose DN.
Schlusselberg D: *see* Gale JT.
Schneider RR, Pichard AD, Mindich B: Factors predisposing to intraoperative myocardial infarction during coronary artery bypass surgery, 52(2):123–129.
Schwartz AM, Leonidas JC, Doku CH: Aggressive juvenile fibromatosis, 52(5):378–379.
Schwartz IS: Surgical Pathology notes ed., *see* Surgical Pathology Notes; *see* also Loiterman DA; Rosen-Leven EM.
Seife B: *see* Diakoumakis E.; Waxman JS.
Seminars for Congressional aides: an educational program on the role of the urban academic medical center, Glenn JF, Grupenhoff JT, Levinson PS, 52(9):736–739.
Senile macular degeneration and Kuhnt-Junius degeneration as separate entities: review, Levitan M, Gombos GM, Levitan H, Levitan LJ, 52(8):663–666.
Sevush S, Turkewitz LJ: Brain biopsy: risks, benefits, and indications, 52(5):380–383.
Shafir M: guest ed., New frontiers in surgical oncology, 52(3):158–232; Immune complexes in cancer and preneoplastic disease, 52(3):201–204; Summary, New frontiers in surgical oncology, 52(3):207; What is cancer surgery? 52(3):165–171.
Sharma OK: *see* Fischebein A.
Sherry HS: Orthopedic oncology, 52(3):189–190.
Sherzer A: *see* Ismajovich B.
Should mild hypertension be treated? An attempted meta-analysis of the clinical trials, Sacks HS, Chalmers TC, Berk AA, Reitman D, 52(4):265–270.
Silvaroli M: *see* Caruso U.
Silvay G, guest ed., Cardiac anesthesia: three decades, 52(7):499–564; Introduction, 499.
Silvay G, Koffsky RM: Mechanical support of the failing heart, 52(7):548–552.
Silver AL; *see* Rose DN.
Sinus node dysfunction: new concepts and evaluation of patients with suspected sick sinus syndrome, Gomes JA, 52(8):610–617.
Skogerson KE, Fredland AJ, Airan MC: Gastric inflammatory pseudotumor, 52(8):661–662.
Skovron ML: *see* Mulvihill MN.
Skovron ML, Goldberg E, Suljaga-Petchel K: Factors predicting survival for six months after cardiopulmonary resuscitation: multivariate analysis of a prospective study, 52(4):271–275.
Snyder TC: *see* Diakoumakis E.
Solitary cecal ulcer due to cytomegalovirus in a leukemic patient, Rosen-Levin EM, Schwartz IS, 52(2):139–141.
Solitary neurofibroma of the gallbladder: report of three cases and literature review, Ilie B, Behar AJ, 52(6):473–477.
Some effects of a hospital employee strike on patient satisfaction, Rosenberg G, Speedling EJ, Rehr H, Morrison BJ, 52(4):259–264.
Speedling EJ: *see* Rosenberg G.
Squire A, Kupersmith J: Beta adrenergic blocking agents: review and update, 52(7):553–558.
Stam M, Strain JJ: Refusal of treatment: role of psychiatric consultation, 52(4):306–309.
Stern TA: Management of depression and anxiety following myocardial infarction, 52(8):623–633.
Stollman AL, Train JS, Dan SJ, Mitty H: Percutaneous transhepatic placement of a biliary endoprosthesis, 52(5):395–397.
Strain JJ: *see* Stam M.
Stress, pancreatic perfusion, and acute pancreatitis: unified concept of pathogenesis, Kaplan MH, 52(5):326–330.
Student Award 1984/85: Gennuso R, 52(6):414.
Suljaga-Petchel K: *see* Lefkowitz P.; Mulvihill MN; Skovron ML.
Summary: New frontiers in surgical oncology, Shafir M, 52(3):207.
Surgery Notes: Gastric inflammatory pseudotumor, Skogerson KE, Friedland AJ, Aivar MC, 52(8):661–662.
Surgical oncology, new frontiers in, Shafir M, guest ed. 52(3):158–232.
Surgical Pathology Notes: Malignant fibrous histocytoma of the maxillary sinus, Unger PD, Kaneko M, Thung SH, 52(7):569–574; Malignant histiocytosis, Plous R, 52(6):496–498; Solitary cecal ulcer due to cytomegalovirus in a leukemic patient, Rosen-Levin EM, Schwartz IS, 52(2):139–141.

Tetralogy of fallot: historical lessons, Fuster V, Griepp RB, 52(7):534–540.
Tey PH, Ahmed A, Chan KF: Case report: Milk of calcium in the kidney after cyst puncture, 52(8):659–660.
Thomas RI, Aguillaume CJ: Role of research and public policy in the regulation of methadone maintenance programs, 52(9):
Thomas W: Pathology Notes ed. *see* Pathology Notes.
Thompson RW: *see* Wong PS.
Thornton J: *see* Gleicher N.
Thoughts on the surgical staging of lymphomas, Norton L, 52(3):185–188.
Three decades of cardiac anesthesia, Arens JF, 52(7):516–520.
Thung SH: *see* Unger PD.
Thyroid disease in pregnancy and the postpartum period, Davies TF, Cobin R, 52(1):59–77.
Thys DM: Monitoring the left ventricle: volume versus pressure, 52(7):526–528; *see* Konstadt S.
Tisone G: *see* Caruso U.
Toledano A: *see* Salinas A.
Tolentino AO, Javier RP, Samet P: Electrocardiographic patterns of normally functioning dual chamber pacemakers, 52(2):116–122.
Torino FD, Portillo NA, Romero OA, Garaycoechea ME, Deluca E, Perera SG: Preliminary observations on application of ethibloc in necrohemorrhagic acute pancreatitis in humans, 52(5):343–346.
Toth E: *see* Salinas A.
Train JS: Interventional radiology of the biliary tree: Introduction, 52(5):387–388; *see* Lewin B.; Lidov M.; Stollman AL.
Treatment of hepatic metastases, Jones RB, 52(3):176–180.
Triebling AT: *see* Dreiling DA.
Tsang PH, Holland JF, Bekesi G: Tumor-associated immunity and serum blocking by radioisotopic leukocyte adherence inhibition assay, 52(3):193–200.
Tuberculosis chemoprophylaxis for diabetics: are the benefits of isoniazid worth the risk? Rose DN, Silver AL, Schechter CB, 52(4):253–258.
Tumor-associated immunity and serum blocking by radioisotopic leukocyte adherence inhibition assay, Tsang PH, Holland JF, Bekesi G, 52(3):193–200.
Tumor growth kinetics, Norton L, 52(3):161–164.
Turkewitz LJ: Neurology Notes ed., *see* Neurology Notes; *see* also Ruderman MI; Sevush S.

Ullman H: *see* Rosenbloom BE.
Unger PD, Kaneko M, Thung SH: Malignant fibrous histocytoma of the maxillary sinus, 52(7):569–574.
Uribarri J, Oh M, Carroll HJ: Hypertension in the elderly, 52(8):581–593.

Valvular heart disease in the elderly, Berman ND, 52(8):594–600.
Venous air embolism: case report and review, Raskin JM, Benjamin E, Iberti TJ, 52(5):367–370.
Vermesh M: *see* Gleicher N.
Vieux U: *see* Diakoumakis E.

Wallace DJ: Globus award 1984/85, 52(6): 415; Wallace DJ: Photograph, 52(6):415.
Wasser WG, Grishman E, Goldstein MH, Gerber M: Recurrent nephropathy associated with heroin use, 52(5):375–376.
Waxman JS, Seife B, Waxman M: Hepatocellar carcinoma presenting as sphenoid sinus metastasis, 52(3):221–224.
Waxman M: *see* Waxman JS.
Waxman S: guest ed., Combination cancer chemotherapy, 52(6):405–469; Introduction, 52(6):405–469.
Weed LL: Computer as a new basis for analytic clinical practice: coupling individual problems with medical knowledge, 52(2):94–99.
Weinstein IM: *see* Rosenbloom BE.
Weisbrod BA: *see* Goddeeris J.
Wexler MC: *see* Wong PS.
What is cancer surgery? Shafir M, 52(3):165–171.
What we don't know about why health expenditures have soared: interactive effects of insurance and technology, Goddeeris J, Weisbrod BA, 52(9):685–692.
Wilder JR: *see* Keller SM.
Williams JS: *see* Mathiot M.
Wolf, CW, guest ed, Computer in clinical decision making, 52(2):79–157; Introduction, 52(2):79.
Wong PS, Rosemark PJ, Wexler MC, Greenberg SH, Thompson RW: Doses to organs at risk from mantle field radiation therapy using 10 MV X-rays, 52(3):216–220.
Wormsley KG: *see* Davey PG.

Zinn KM: Ophthalmology Notes ed., *see* Ophthalmology Notes.

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